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BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

[Vol. XXI.—No. 228.] BALTIMORE, MARCH, 1910. Price, 25 Cents

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STUDIES ON ISOAGGLUTININS AND ISOHEMOLYSINS.

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The hemoglobin may be set free from the red blood corpuscles by a variety of influences; as mechanical injury, extremes of temperature, variations in the tonicity of the medium in which they are placed, acids, alkalies, soaps, bacterial and other plant hemotoxins, etc. Likewise corpuscles agglutinate under a variety of influences but in the work to be reported in this paper care has been taken to exclude all agglutinating and hemolysing influences except those possessed by the serum.

Serum agglutinins and hemolysins may be designated as normal and immune, according as they exist in the blood of animals in their natural state or have resulted from the artificial introduction of blood from one animal into another. The serum of many animals normally possesses the power of agglutinating and dissolving the corpuscles of animals of a different species, due to the presence of normal heteroagglutinins and heterohemolysins. This power may be greatly increased by the injection of foreign red blood corpuscles, the immune heteroagglutinin and heterohemolysin thus produced, however, being in a high degree specific for the particular kind of red blood corpuscles used in their production.[1]

The prefix iso- is used to designate that variety of agglutinin and hemolysin which is effective against the erythrocytes of another animal of the same species as that possessing the agglutinin and hemolysin. Isoagglutinins and isohemolysins may be normal: i. e., occurring naturally; or immune, resulting from the injection of red blood corpuscles of an animal into another animal of the same species.

Auto- is the prefix applicable to agglutinins and hemolysins capable of clumping and dissolving the corpuscles of the animal possessing such "bodies." We have a well recognized example of autohemolysin in certain forms of paroxysmal hemoglobinuria, but with the peculiarity that the amboceptor unites with the corpuscles only at certain low temperatures while the complement does not combine except at higher temperatures.

This paper deals with normal isoagglutinins and isohemolysins occurring in the serum of man. Ehrlich and Morgenroth (Studies on Hemolysins. Berlin. klin. Wchnschr., 1900, No. 21) were able to produce isohemolysins in animals by the injection of the blood of one goat into another, but in no case were they able to demonstrate autohemolysins following the injection of an animal with its own corpuscles.

[1] It is likely that the normal agglutinin and hemolysin are also specific. If one takes a serum which is able to agglutinate or hemolyse two different varieties of corpuscles and allows it to act on a sufficient quantity of one variety, all of the agglutinin or hemolysin for that variety can be absorbed without lessening the ability of the serum to agglutinate or hemolyse the other variety of corpuscle.

A few observers have reported the finding of normal isoagglutinins and isohemolysins in animals, but their occurrence is rare as compared with the frequency with which they may be found in man. Indeed Hektoen (J. Infect. Dis., 1907, Vol. IV, p. 297), states that he has "not been able to find any isoagglutinins in the serum of rabbits, guinea-pigs, dogs, horses, and cattle," although "the serum of the majority of healthy individuals above six years of age contains isoagglutinins."

Numerous attempts have been made to establish some relation between the occurrence of isoagglutinins and isohemolysins, and various diseases, but so far the claims of investigators who maintain that such relations exist are not borne out by the accumulated evidence. It seems likely that the misleading results of many of these observers have been due to the fact that they have based their conclusions upon the action of the sera investigated upon corpuscles from too small a number of individuals, for it has been definitely established that a given serum may agglutinate or hemolyse the corpuscles of certain individuals and not those of others, so that the results obtained in any series of cases would depend largely upon the corpuscles employed in the test. For this reason, in all of my investigations, the serum of each member of a series was tested against the corpuscles of every other member of the series; and the occurrence or absence both of agglutination and hemolysis noted.

Furthermore certain of the discordant results probably have been due to variations in the technique used. Some of the earlier observers were content merely to bring together equal quantities of the defibrinated blood of two individuals and observe the results. In such tests the possible interaction of four elements was present; namely, two different sera, and two different kinds of corpuscles, instead of the action of a single serum on a single kind of corpuscle; a matter of importance, as will be shown later, on account of the inhibiting action which certain sera are capable of exerting on hemolysis.

The technique employed in all of the tests here reported was carried out with surgical asepsis, and great care was taken that the syringe, pipettes, test-tubes, and all glassware used were not only sterile but very clean. Blood is taken from a vein at the elbow. For this purpose the skin over the vein is rendered aseptic and about 20 cc. of blood is withdrawn by means of a syringe which previously has been boiled and then washed out with a solution containing 1.5 per cent sodium citrate and 0.85 per cent sodium chloride; this removes any water which remains in the syringe after boiling and which might cause slight laking of the blood. Two sterile centrifuge tubes are ready to receive the blood as soon as it is withdrawn, one being empty and the other containing 10 or 12 cc. of 1.5 per cent sodium citrate in 0.85 per cent sodium chloride solution. Into the tube containing the sodium citrate, 3 cc. of blood is introduced for corpuscles, and the remaining blood is put into the other tube for serum. The corpuscles are further prepared by centrifugalizing them out of the sodium citrate solution, pipetting off the supernatant fluid and washing them twice with 0.85 per cent sodium chloride solution to free the cells from serum. After the last centrifugalization, which is continued until the cells are thoroughly sedimented, the supernatant fluid is pipetted off and 0.5 cc. of the corpuscles is transferred to 9.5 cc. of 0.85 per cent sodium chloride solution, thus making a 5 per cent suspension.

The tube containing the blood for the serum is allowed to clot and after about half an hour the clot is carefully separated from the sides of the tube with a sterile platinum needle, after which the serum is easily obtained by a few minutes' centrifugalization. The clear serum is then pipetted off from the clot and transferred to another tube. Serum and corpuscles are similarly obtained from a number of individuals.

The further proceedure consists in combining equal quantities (usually 0.25 or 0.5 cc.) of serum and suspension of corpuscles so that the action of each serum is tested on the corpuscles of every member of the series separately These mixtures having been made, the tubes are shaken to distribute the corpuscles evenly through the serum, and are then allowed to stand in the thermostat at 37.5° C. for 2 hours, after which they are placed in the icechest over night. Readings are made at the end of the two hours in the thermostat and after the tubes have stood over night in the icechest. Agglutination and hemolysis are easily determined by the naked eye, and the results of the reading at the end of two hours in the thermostat and after having stood over night in the icechest differ, if at all, only slightly in amount.

Before examining the results obtained, it may be stated that no constant differences were found between the agglutinating or hemolysing abilities of sera in health and in disease. The serum of a healthy individual might agglutinate or hemolyse the corpuscles of some healthy individuals, but fail to agglutinate or hemolyse those of other healthy individuals, and the same variations were noted in its action on the corpuscles of patients suffering from a variety of diseases. The same relations were found to exist between the serum in disease and the corpuscles of diseased and healthy individuals. Tests have been carried out on the blood of 213 individuals of whom 97 were healthy, and 116 diseased. In the case of 22 of the healthy individuals the blood was tested from two to 5 times, at intervals of a few days, weeks, or months. The agglutinating action of these sera was found to be constant, but the hemolytic power varied in some of them from time to time. On five occasions series of 20 individuals were tested. In these series the serum of each individual was tested against the corpuscles of every other individual, including his own—a total of 400 tests in each series. Certain results were obtained from these large series which might have been missed in smaller ones.

In about half of the total number of cases examined the tests were carried out on groups of eight individuals at a time, the serum of each one being tested against the corpuscles of each member of the series, making a total of 64 individual tests. When examining patient's blood, the serum was often tested against corpuscles from a number of normal in-

dividuals. The ability of patient's serum to hemolyse and agglutinate normal corpuscles; of normal serum to hemolyse and agglutinate patient's corpuscles; and furthermore the presence or absence of autolysis and autoagglutination in both patients and normal blood was noted.

It would require too much space to include here the individual results, but they have been summarized and are tabulated in convenient form.

TABLE I.

No. Cases.	Disease.	Pat. Ser. Nor. Corps. Hem.	Pat. Ser. Nor. Corps. Aggl.	Nor. Ser. Pat. Corps. Hem.	Nor. Ser. Pat. Corps. Aggl.	Pat. Ser. Pat. Corps. Autol.	Pat. Ser. Pat. Corps. Autoaggl.	Nor. Ser. Nor. Corps. Autol.	Nor. Ser. Nor. Corps. Autoaggl.
35	Tuberculosis. Various forms....	8	14	7	10	0	0	0	0
27	Carcinoma.....	4	6	6	8	0	0	0	0
14	Typhoid fever.....	3	5	1	5	0	0	0	0
10	Chronic nephritis..	1	3	2	4	1	0	0	0
6	Diabetes mellitus..	0	2	3	2	0	0	0	0
5	Pernicious anemia.	1	0	3	2	0	0	0	0
4	Lues	1	2	0	0	0	0	0	0
83	Other diseases	8	24	12	25	0	0	0	0
		26	56	34	56	1	0	0	0

Examination of Table I shows that normal serum was able to hemolyse and agglutinate patient's corpuscles as often as patient's serum was able to hemolyse and agglutinate normal corpuscles; that this relation does not differ markedly in different diseases, and furthermore that autoagglutination did not occur in a single instance, while autolysis occurred only once. This latter case requires closer examination. The blood was from a chronic nephritic who was in uremia at the time the test was made. The solution of his corpuscles was but slight in extent and not accompanied by agglutination which leads me to think that the hemolysis was not due to a specific amboceptor-complement action, but perhaps to some toxic substance circulating in the blood, of a chemical nature.

The serum of this patient not only hemolysed his own corpuscles, but those of all of the seven other individuals against which it was tested, and in no case did it cause agglutination.

We have seen thus far that the agglutinating and hemolysing action of patient's serum on normal corpuscles does not differ in any marked degree from the action of normal serum on patient's corpuscles. In order to complete this study, it is necessary to investigate the action of normal serum on normal corpuscles and of patient's serum on patient's corpuscles. For this purpose two series of 19 patients each, suffering from a variety of diseases were taken and the serum of each one was tested against the corpuscles of every other member of the series as well as the autogenous corpuscles. Similarly three series of 19 or 20 healthy individuals were tested.

The results are given in Tables II and III. They show no important differences between the action of patient's serum on patient's corpuscles, and the action of normal serum on normal corpuscles. Furthermore these two reactions—patient's serum on patient's corpuscles and normal serum on normal corpuscles, do not differ markedly from the relations brought out in Table I where patient's serum was tested against normal corpuscles and normal serum against patient's corpuscles.

TABLE II.

		Number whose serum agglutinated or hemolysed the corpuscles of one or more members of the series. Agglutinated.	Hemolysed.
1st Series	19 patients.	18	1
2d "	19 "	17	8
	38	35	9

TABLE III.

		Number whose serum agglutinated or hemolysed the corpuscles of one or more members of the series. Agglutinated.	Hemolysed.
1st Series	20 normals.	19	11
2d "	20 "	18	0
3d "	19 "	16	3
	59	53	14

From Tables II and III we see that of 59 normal sera tested, 53 (89+ per cent) agglutinate and 14 (23+ per cent) hemolyse as compared with the sera of 38 patients in which 35 (92+ per cent) agglutinate and 9 (26+ per cent) hemolyse, from which we may draw the conclusion that there is no marked difference between the isoagglutinating or isohemolytic action of the serum in health and disease, and while some still claim that one or the other of these reactions may be made use of in the diagnosis of various diseases, I must agree with those who maintain that they have no diagnostic significance. It is true that the individual series in any one disease here studied is not large, but collectively they seem sufficient for the above generalisation.

Certain other points in regard to isoagglutinins and isohemolysins, perhaps, only of theoretical interest, have been studied in some detail.

Landsteiner (*Ueber Agglutinationserscheinungen normalen menschlichen Blutes.* Wien. klin. Wchnschr., 1901, XIV, p. 1132) in 1901 denied the specificity of the isoagglutination reaction for disease and pointed out that the phenomenon is also produced by the serum of healthy individuals and goes so far as to attempt a classification of sera according to their isoagglutinating action. His classification, which has been generally accepted up to this time, makes three groups as follows: "In a number of cases (Group A) the serum agglutinates the corpuscles of another Group (B) not, however, those of Group A; while the corpuscles A are agglutinated by the serum B. In the third Group (C) the serum agglutinates the corpuscles of A and B." That this classification is imperfect is shown by attempting to apply it to any of the series of 20 individuals in which I have tested each serum against the corpuscles of every member of the series.

One such series will suffice to point out the difficulties of its application.

TABLE IV.

CORPUSCLES. \ SERUM.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1					+		+	+	+		+	+		+	+		+			+
2					+		+	+	+		+	+		+	+		+			+
3					+		+	+	+		+	+		+	+		+			+
4	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
5																				
6	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
7	+	+	+		+			+	+	+	+	+	+	+	+	+	+		+	+
8																				
9																				
10					+		+	+	+		+	+		+	+		+			+
11																				
12																				
13					+		+	+	+		+	+		+	+		+			+
14																				
15																				
16					+		+	+	+		+	+		+	+		+			+
17																				
18	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
19					+		+	+	+		+	+		+	+		+			+
20																				

By tabulating Landsteiner's classification in a more convenient form, we get the following statement of it:

Group A. Serum agglutinates corpuscles of Group B.
Corpuscles agglutinated by serum of Groups B and C.

Group B. Serum agglutinates corpuscles of Group A.
Corpuscles agglutinated by serum of Groups A and C.

Group C. Serum agglutinates corpuscles of Groups A and B.
Corpuscles not agglutinated by serum of Groups A and B.

On examining the classification we see that the sera of all three groups are capable of agglutinating the corpuscles of some other group, that the corpuscles of Groups A and B are agglutinated by the sera of some other group, while it is not stated that the corpuscles of Group C are agglutinated by any serum. This gives one a starting point for the application of the classification.

In the series shown in Table IV we see that the corpuscles of a certain number of individuals have not been agglutinated by any serum. These individuals clearly cannot be placed in Group A or B because the corpuscles of the members of these groups are agglutinated. They may then belong in Group C, since it is not stated that the corpuscles of the members of this group are agglutinated at all.

One may then provisionally place in Group C all those members of the series whose corpuscles are not agglutinated at all. The remaining members of the series would then fall in Groups A and B. Thus we have:

Group C = 5, 8, 9, 11, 12, 14, 15, 17, 20.
Groups A and B = 1, 2, 3, 4, 6, 7, 10, 13, 16, 18, 19.

If we look at Table IV, we will see that the sera of all those whom we have placed in Group C do agglutinate the corpuscles of all those in Groups A and B, thus fulfilling the requirement for this group.

We have now to separate Groups A and B, and since the relations which these two groups bear to each other, are reciprocal, and the relations they bear to Group C are identical, we can arbitrarily select any one of the combined Groups, A and B, and place it in Group A and by applying the requirements of the classification, we can separate the members of Group B. For example let us place No. 1 in Group A. The requirements are that the serum of No. 1 shall agglutinate the corpuscles of Group B, and by examining the action of serum No. 1 on the corpuscles of the rest of the members of the combined Groups A and B, we find that it agglutinates the corpuscles of Nos. 4, 6, 7, 18. Hence we will place 4, 6, 7, 18 in Group B. Now the remainder of the combined Groups A and B must, if the classification is correct, belong in Group A. Group A will then consist of Nos. 1, 2, 3, 11, 13, 16, 19. According to the classification, the sera of all of these should agglutinate the corpuscles of Group B, and the corpuscles of this group should be agglutinated by the sera of Groups B and C.

By referring to Table IV, we find that the first of these requirements is fulfilled; namely, that the sera of Group A shall agglutinate the corpuscles of Group B, and that the corpuscles are agglutinated by the sera of all of the members of Group C, but, when we come to the requirement that they shall also be agglutinated by the sera of Group B, we find that they are agglutinated by serum No. 7, but not by Nos. 4, 6, 18. The requirements for Group B are fulfilled, with the same exception, namely, that sera Nos. 4, 6, and 18 do not agglutinate the corpuscles of Group A.

In attempting to apply this classification to each of the five series of twenty individuals, exceptions were always encountered, hence, a classification was sought which would cover all cases and to which there would be no exceptions. I found that such a classification required a separation into four groups, and I propose the following to which I have found no exceptions in the last 1600 tests:

Group I. Sera agglutinate no corpuscles.
Corpuscles agglutinated by sera of Groups II, III, IV.

Group II. Sera agglutinate corpuscles of Groups I, III.
Corpuscles agglutinated by sera of Groups III, IV.

Group III. Sera agglutinate corpuscles of Groups I, II.
Corpuscles agglutinated by sera of Groups II, IV.

Group IV. Sera agglutinate corpuscles of Groups I, II, III.
Corpuscles agglutinated by no serum.

Applying this classification to Table IV, we get the following separation:

Group I = Nos. 4, 6, 18.
Group II = " 1, 2, 3, 10, 13, 16, 19.
Group III = " 7.
Group IV = " 5, 8, 9, 11, 12, 14, 15, 17, 20.

Of the 100 bloods tested in series of 20 each, there have been found:

10 belonging to Group I.
40 " " " II.
7 " " " III.
43 " " " IV.

From this it is probable that Group III is the rarest, with Group I but little less infrequent, while Groups II and IV are about equally common.

It has been suggested that isoagglutination and isohemolysis may present a possible danger in the transfusion of blood from one individual to another.

Reference to the classification indicates that so far as agglutination is concerned, it probably would be safe to transfuse between members of any one group; at least, we can say that agglutination outside the body does not take place when the serum of any member of a group is added to the corpuscles of another member of the same group. If agglutination does constitute a source of danger in transfusion, one can see that a risk is run if one undertakes to transfuse from any member of one group to any member of another group, and that the risk is a double one when transfusion takes place between Groups II and III, since then the serum of both donor and donee is capable of agglutinating the corpuscles of the other.

A word in anticipation of a subject to be dealt with when we come to consider isohemolysis may be added here. In transfusion, among other things, we have to deal with the action of the serum of one individual on the corpuscles of another individual in the presence of the second individual's serum, and the first individual's corpuscles. Consequently numerous tests have been made to see if this condition inhibits agglutination. So far it has not been found to do so.

Having shown that individuals can be divided into four groups, according to the ability of their serum to agglutinate the corpuscles of other individuals and according to the ability of their corpuscles to be agglutinated by the serum of other individuals, my next study was to determine, if possible, upon what these differences depend.

In this work I have accepted Ehrlich's theory as being correct. This theory, as applied to the agglutination of red blood cells, assumes that the corpuscles in order to be agglutinated must possess receptors which are capable of uniting with a body which may be present in some sera called an agglutinin. Cells thus united to agglutinin are attracted to each other, come together and cohere in clumps, giving rise to the familiar phenomenon of agglutination. Now, if there is only one kind of hemagglutinophilic receptor, and one kind of isohemagglutinin, the corpuscles of any individual possessing such receptors will be agglutinated by any serum containing such agglutinin. That this is not the case can readily be seen by reference to Table IV, in which, for example, corpuscles of individual No. 1 possess receptors, as is shown by the fact that they are agglutinated by the serum of Nos. 5, 7, 8, etc., moreover serum No. 2 contains agglutinin since it is able to agglutinate corpuscles Nos. 4, 6, 18, etc. But corpuscles No. 1 are not agglutinated by serum No. 2, hence, we have to assume that the receptors of corpuscles No. 1 do not have an affinity for the agglutinin contained in serum No. 2. In other words, either the receptors of corpuscles No. 1 differ from the receptors of corpuscles Nos. 4, 6, 18, etc., or the agglutinin contained in serum No. 2 differs from the agglutinin contained in sera Nos. 5, 7, 8, etc.

If we postulate different kinds of agglutinophilic receptors, it follows that we must postulate different kinds of agglutinins and vice versa. Landsteiner (loc. cit.) reached the conclusion from his results that there were at least two kinds of agglutinin present in the serum in his cases, the one in Group A, the other in Group B, and both in Group C. My results have led me to somewhat different conclusions, and therefore I wish to present the evidence which I have obtained. I shall designate the different kinds of receptors by the small letters a, b, c, etc., and the different kinds of agglutinins by the large letters A, B, C, etc., in which it is intended to indicate that an affinity exists between receptors and agglutinin of like letters. Now, what is it necessary to assume in order to account for the existence of the four groups into which I have divided individuals? There are two (perhaps more) possibilities which would account for the facts which we observe.

First Possibility.

Group I = 4, 6, 18.	Serum contains no agglutinin. Corpuscles possess Recep., a.	Agglutinated by sera of Groups II, III, IV.
Group II = 1, 2, 3, 10, 16, 19.	Serum contains agglutinin A and C. Corpuscles possess Recep., b.	Agglutinates corpuscles of Groups I, III. Agglutinated by sera of Groups III, IV.
Group III = 7.	Serum contains agglutinin A and B. Corpuscles possess Recep., c.	Agglutinates corpuscles of Groups I, II. Agglutinated by sera of Groups II, IV.
Group IV = 5, 8, 9, 11, 12, 13, 14, 15, 17, 20.	Serum contains agglutinin A, B and C. Corpuscles possess no Recep.	Agglutinates corpuscles of Groups I, II, III. Agglutinated by none.

Or Second Possibility.

Group I. Serum contains no agglutinin. Corpuscles possess Recep., a, b and c.

Group II. Serum contains agglutinin A. Corpuscles possess Recep., b and c.

Group III. Serum contains agglutinin B. Corpuscles possess Recep., a and c.

Group IV. Serum contains agglutinin C. Corpuscles possess no Recep.

The problem now is to determine which of these two possibilities represents the true state of affairs. If the first possibility, then the serum of Group IV after absorption with the corpuscles of Group I will still be able to agglutinate the corpuscles of Groups II, III. If the second possibility, then the serum of Group IV after absorption with the corpuscle of Group I will not be able to agglutinate the corpuscles of Groups II, III.

The following single example will serve as an illustration of tests carried out to decide this point. To 1 cc. of serum 5 (Group IV) was added 0.1 cc. of corpuscles 4 (Group I) and the mixture allowed to stand in the thermostat for 1 hour. At the end of this time the corpuscles were found to be agglutinated into a solid mass. The clear supernatant fluid was then pipetted off from this tube and the following tests made with it.

Supernatant fluid.	5% susp. Corps.	Agglutination after 2 hrs. at 37° C.
(1) 0.25 cc.	Gr. I: No. 4 0.25 cc.	0
(2) 0.25 cc.	Gr. II: No. 1 0.25 cc.	0
(3) 0.25 cc.	Gr. III: No. 7 0.25 cc.	0

Test No. 1 showed that all of the agglutinin for corpuscles of Group I had been removed, while tests 2 and 3 showed that all of the agglutinin for Groups II and III had also been removed, indicating that the second rather than the first possibility represents the actual conditions. Thinking that perhaps too large a quantity of corpuscles of Group I had been used for the absorption, and that they might have mechanically removed the agglutinin for the other two groups, the experiment was repeated, using varying amounts of corpuscles for absorption until an amount of corpuscles of Group I was obtained which did not quite remove all of the agglutinin for Group I. Under these conditions it was found that the agglutinin for Group II and III had been extracted to the same extent as that for Group I, thus further indicating the correctness of the second possibility. However, I wish to repeat these experiments a number of times to guard against the possibility of error before affirming that the explanation given is correct.

I have not yet been able to classify individuals according to the isolytic action of their blood as has been done in the case of the isoagglutinative action. That there is a relationship between isoagglutinins and isohemolysins seems likely although this relationship may not extend further than their possible dependence upon a common causative factor.

What this causative factor is, we do not know. Some investigators have advanced the theory that the resorption of blood or its disintegration products stimulate the production of isoagglutinins and isohemolysins in man. We know that there is a physiological blood destruction going on constantly, and that in various morbid states, non-bacterial as well as bacterial, there is a pathological blood destruction, but no satisfactory proof has been brought forward that man responds to the resorption of his own blood, or its disintegration products by the production of agglutinins or hemolysins. The animal experiments along this line have been negative except in the hands of one or two investigators. Ehrlich and Morgenroth, as previously stated, were able to produce immune isohemolysins by the injection of the blood of one goat into another goat, but not by injecting into a goat its own blood. Moreover, Halban (*Agglutinationsversuche mit mütterlichem und kindlichem Blute.* Wien. klin. Wchnschr., 1900, XIII, p. 545) showed that fetal blood taken from the cord at birth often contained isoagglutinins even in cases where the maternal blood was shown to contain no isoagglutinin. In such cases it would be hard to refer the presence of the isoagglutinin in the child's blood to the resorption of blood which had undergone destruction under pathological influences, and since the maternal blood contained no isoagglutinin, it could not have been derived from that source.

Without inquiring more closely into the ultimate causative factor upon which isoagglutinin and isohemolysin depend, the view which I have suggested that they may depend on a common causative factor is strengthened by the work of Ford and Halsey (Contributions to the Study of Hemagglutinins and Hemolysins. J. Med. Research, 1904, Vol. VI), who showed, contrary to certain other observers, that agglutinins and hemolysins could not be produced independently by the injection of the stroma of red blood corpuscles or hemoglobin alone. When hemoglobin-free stroma was injected into suitable animals, they found that both agglutinins and hemolysins were produced and that the same result followed the injection of pure hemoglobin.

In regard to the relationship existing between isoagglutinins and isohemolysins, I may say that agglutination frequently occurs independently of hemolysis, but that the inverse relation occurs, i. e., hemolysis without the simultaneous or preceding occurrence of agglutination seems less likely. In my first experiments hemolysis without agglutination was frequently recorded, but closer attention to this point in subsequent experiments led me to doubt the correctness of these earlier observations.

Agglutination is a phenomenon which concerns the corpuscle as a whole, while hemolysis is a phenomenon which destroys the integrity of the corpuscle, and it is possible that agglutination cannot persist among corpuscles which have been damaged by the action of hemolysins. As a rule, however, agglutination proceeds more rapidly than does hemolysis and by observing the action of a serum, which contains both agglutinin and hemolysin, on susceptible corpuscles, one frequently sees agglutination set in which is subsequently broken up as hemolysis takes place; so that if the observations are not made until the lapse of 2 hours, in a case where the hemolysin is not quite sufficient to dissolve completely all of the corpuscles present, we may get the appearance of hemolysis having taken place without agglutination. As indicated in Tables II and III the occurrence of isoagglutinins in man is much more frequent than the occurrence of isohemolysins. In 100 individuals tested, 61 of whom were healthy and 39 suffering from various diseases isoagglutinins were found in 92 cases and isohemolysins in 25 cases. The latter, isohemolysins, have not been found in Group I, that is in those individuals whose serum contains no agglutinin, but have been found in each of the other three groups, Groups II, III, and IV. Moreover the same statement apparently applies to isohemolysins as was made in regard to isoagglutinins; namely, that the serum of any individual of one group may hemolyse the corpuscles of another individual in any other group except Group IV, but not the corpuscles of a member of same group.

In the hundred individuals tested in groups of 20, I have found only two exceptions to this rule, and it seems likely that the hemolysis in these two cases may have been due to accidental causes. A further point of considerable theoretical interest and of practical importance in its bearing on the question of transfusion in man was discovered.

Given an individual, A, whose serum is capable of hemolysing the corpuscles of another individual, B, in the test tube,

the hemolysis is prevented if the serum of B is added to the serum of A before it is allowed to act on the corpuscles B. For this experiment it is best to mix the two sera and allow them to remain in the thermostat for half an hour before adding the corpuscles, but even when the corpuscles are added immediately the inhibition is partial if not complete.

It was further found that the serum of any member of the same group as that to which the individual furnishing the corpuscles belonged would also exert an inhibiting action. Ascoli (*Isoagglutinine und Isolysine menschlicher Blutsera.* Münch. Med. Wchnschr., 1901, Vol. 48, No. 31, p. 1239) was able to show in a certain number of cases that the isolytic action was due to two bodies, one thermostable (amboceptor) the other thermolabile (complement). This he proved by the usual method of heating hemolytic serum to 56° C. for 20 minutes, and showing that it had lost its ability to cause solution of the red blood corpuscles, but that this power could be restored by the addition of the fresh serum of another individual, which serum alone was incapable of producing any hemolysis. Ascoli states that in a certain number of cases he was able to accomplish this reactivation, but in others the reactivation failed for reasons which remained to him inexplicable. I have confirmed Ascoli's statements regarding the amboceptor-complement nature of isohemolysin and of their relations to heat and in the light of the statements I have just made, it seems probable that in the cases where Ascoli was unable to reactivate his hemolytic sera after heating, that he may have been using for the reactivating serum, the blood of an individual belonging to the same group as the individual from whom the corpuscles were taken and that the reactivation failed, not through any lack of complement, but on account of the presence of inhibiting bodies in such a serum. In order to reactivate a given hemolytic serum one may best employ the serum (nonhemolytic) of a member of the same group as that to which the hemolytic serum belongs.

I have tested this property of the serum to inhibit the hemolysis of the homologous corpuscles, or the corpuscles of any member of the same group and found that it resists heating to 57° C. for half an hour, and is therefore thermostable.

I have next attempted to discover the point of action of this inhibiting body. Theoretically such a body might act by combining with, 1, the receptor group of the cells; 2, the cytophilic group of the amboceptor; 3, the complementophilic group of the amboceptor; 4, with the complement.

The first possibility, blocking of the receptor of the cell, can be ruled out at once, for if this occurred, cells first treated with the inhibiting serum and then removed by centrifugalization and washed would not be dissolved on the subsequent addition of a hemolytic serum. We know that the serum of any individual protects its own corpuscles from hemolysis by any other serum, but as soon as the corpuscles are removed from their own serum they may be dissolved by other hemolytic sera, showing that their receptors are free.

To determine which if either group of the amboceptor has been blocked, that is if the antihemolysin is an antiamboceptor, we may proceed as follows: To susceptible corpuscles add inactivated hemolytic serum and inactivated protective serum. After these have stood together for a while in the thermostat remove the corpuscles and wash them. Now if the cytophilic group of the amboceptor has been blocked the receptor group of the corpuscles will remain free, and they may be hemolyzed by the addition of fresh hemolytic serum, but not on the addition of complement alone; but if the complementophilic group of the amboceptor has been blocked the cells may have anchored the amboceptor-antiamboceptor combination and hence will not be hemolyzed on the addition even of fresh hemolytic serum. If the inhibiting body is an anticomplement, the cells after removal and washing should be hemolyzed on the addition of complement alone. In order to determine this point I selected an individual C from Group IV whose serum was hemolytic for the corpuscles of an individual A of Group I. Equal quantities of C's serum and A's serum were inactivated and added to A's corpuscles. After the mixture had stood for an hour in the thermostat at 37.5° C. the corpuscles were removed by centrifugalization, washed, suspended in a small amount of salt solution and to one portion complement alone was added (serum D, Gr. IV which had been shown to possess no hemolysin), and to another portion of the corpuscles fresh serum from C was added. Those corpuscles to which complement alone was added were not affected while those to which hemolysin was added underwent prompt solution showing that the antihemolysin is an antiamboceptor which acts by blocking the cytophilic group of the amboceptor.

At present I am only prepared to speculate as to the origin and nature of this antihemolysin.

Müller (*Ueber die Erzeugung hämolytischer Amboceptoren durch Seruminjection.* Münch. med. Wchnschr., 1902, XLIX, No. 32, p. 1330) refers to the work of Morgenroth in which he showed that by the injection of serum one could call forth the production of hemolytic amboceptors which are identical with those resulting from the injection of blood. Müller refers to his own earlier work in which he showed that a whole series of normal sera possess antihemolytic properties directed against the hemolysins contained in other normal sera. He proceeded to inject sera containing antihemolysin in an effort to produce an anti-antihemolysin, and thought at first that he had succeeded in accomplishing this, but closer scrutiny showed that he had merely produced a hemolytic serum. By injecting guinea-pig serum into another animal he obtained a serum capable of dissolving guinea-pig corpuscles. His explanation of the fact that the injection of serum alone is able to produce an hemolysin is that the serum must contain groups identical with the receptor groups of the corpuscles, and he further suggests that if the serum contains groups identical with the receptor groups of the corpuscles, such a serum should be able to bind the hemolysin and thus protect the corpuscles from hemolysis. I arrived at the same conclusion regarding the nature of the antihemolysin directed against isohemolysin which I observed.

Conclusions.

1. Isoagglutinins occur in the serum of about 90 per cent, and isohemolysins in about 25 per cent, of adult human beings.

2. These bodies appear with approximately the same relative frequency in health and in various diseases and therefore have no diagnostic significance.

3. In a number of healthy individuals whose blood was repeatedly tested at varying intervals of time the agglutinating action was found not to vary, while in some cases the hemolytic action which was present in earlier tests was absent in subsequent tests.

4. There are at least three different isoagglutinins and three isohemolysins in human sera and three different isoagglutinophilic and three isohemolysinophilic receptors possessed by human red blood corpuscles.

5. There are human sera which contain no isoagglutinin and isohemolysin but whose corpuscles possess receptors for isoagglutinin and isohemolysin.

6. No individual serum which I have investigated appears to contain more than one of the three kinds of isoagglutinin or isohemolysin.

7. The corpuscles of a given individual may possess no isoagglutinophilic or isohemolysinophilic receptors or they may possess two, or all three kinds of these receptors.

8. Human beings can be divided into four groups according to the ability of their serum to cause isoagglutination and of their corpuscles to be isoagglutinated.

9. The serum of members of any one group will not agglutinate or hemolyse the corpuscles of other members of the same group but will agglutinate and may hemolyse the corpuscles of members of any other group except those of Group IV. This may have a practical application in the transfusion of blood from one individual to another.

10. Autoagglutination was not observed in any of the 213 cases investigated and autohemolysis was observed only once. In the latter case the hemolysis may have been due to extraneous causes.

11. A strict classification of individuals according to the isohemolytic action of the blood has not been accomplished.

12. Isoagglutination may occur independently of isohemolysis but isohemolysis is probably always preceded or accompanied by isoagglutination.

13. All the sera investigated contained an antihemolysin which protected the homologous corpuscles and those of members of the same group from solution by any other serum.

14. This antihemolysin is an antiamboceptor which acts by uniting with the cytophilic group of the hemolysin thus blocking it off from the red blood cell; and probably consists of receptor groups of the red blood cells which have been cast off from the cells or set free by the physiological or pathological destruction of the corpuscles.

15. Isoagglutinin is thermostable; that is it resists heating to 55° C. for 30 minutes.

16. Isohemolysin consists of two components; one, thermostable, resisting heating to 55° C. for 30 minutes (amboceptor), the other thermolabile, destroyed by heating to 55° C. for 30 minutes (complement).

17. The antihemolysin is thermostable, resisting heating to 55° C. for 30 minutes.

18. Any non-lytic serum may be used to reactivate an inactivated hemolytic serum provided the reactivating serum does not contain antihemolysin against the amboceptor of the hemolytic serum. In other words the reactivating serum must not be chosen from the same group as that to which the corpuscles to be hemolyzed belong. The reactivating serum may best be chosen from the same group as that to which the hemolytic serum belongs.

19. The origin of isoagglutinin and isohemolysin has not yet been satisfactorily determined. It probably cannot be referred to the destruction and resorption by an individual of his own blood.

Note.—Since the above paper went to press there has come to my notice in the *Jahresbericht für Neurologie und Psychiatrie*, 1907, the review of a paper by Jan. Janský, entitled "Haematologische Studien bei Psychotikern," *Klinický Sbornik*, No. 2, 1907; in which the author divides individuals into four groups according to the agglutinating reaction of the blood quite in the same way that I have done, except that his Group I corresponds to my Group IV and *vice versa*.

Had this paper come to my notice in time I could have given the author credit in the body of my paper for his priority in establishing the correct classification.

CLINICAL EXPERIENCE WITH THE WASSERMANN REACTION IN THE JOHNS HOPKINS HOSPITAL.

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I.

The great importance of an accurate method for the diagnosis of syphilis in its obscure forms is a matter of general recognition. Though in the strictest sense a constitutional disease, a definite diagnosis has hitherto been impossible in a considerable number of cases which did not happen to show some cutaneous or other external manifestation. Hence the announcement by Wassermann of the discovery of a reliable method of serum diagnosis aroused unusual interest and led to a very large amount of confirmatory work.

As originally devised by Wassermann in 1906,[1] the test depended on the principle of complement fixation formulated

by Bordet and Gengou in 1901.[2] They found that if a bacterial culture was added to the fresh blood serum of an animal immunized to that organism, the complement present in the serum would be removed, or fixed, so that it would no longer be able to dissolve sensitized red blood corpuscles.

If a rabbit is injected with the red blood corpuscles of a sheep, the blood serum of the rabbit will acquire the power of dissolving the sheep's corpuscles. This power of dissolving the sheep corpuscles is not present in normal rabbit serum, but only in that of the treated animal. It is specific. That is, it is effective only in dissolving the corpuscles of that one species of animal, the sheep. It will not dissolve those, for example, of the ox, the dog, or the chicken. In order to carry out this solution, the rabbit serum must be fresh. If it is old, or if heated to 56° C. for 20 minutes, it will lose this power, but will regain it if a little fresh serum is added from any normal animal, as e. g. from a guinea-pig. Such a solution, then, depends on the presence of two substances. One, not present in normal rabbits, but formed as a result of the injection of sheep corpuscles, is called the amboceptor, immune body, or hæmolysin. It is specific, and since it is not destroyed by heating, is said to be thermostabile. The serum containing it is known as an hæmolytic serum. The second, present in all sera, and destroyed by heating, is called complement. Corpuscles which have been mixed with an inactivated specific hæmolytic serum, such as the rabbit serum just described, are said to be sensitized; they are so changed as to be dissolved on the addition of free complement. For the purposes of this reaction, they may be regarded simply as a reagent for the detection of free complement in a solution, hæmolysis occurring, if free complement is present.

Any substance, bacterial or otherwise, which on injection into an animal, results in the production of specific antibodies is known as an antigen.

Bordet and Gengou showed that if an emulsion of typhoid bacilli (an antigen) is added to the fresh serum of an animal immunized to typhoid (and containing specific antibodies), the serum would lose its power of dissolving sensitized corpuscles, due to the removal or fixation of its complement. They found this phenomenon to be specific. If any serum was used except one immune to the particular organism with whose culture it was mixed, the complement would not be disturbed and the serum would retain its power of dissolving the sensitized corpuscles. They devised the test for detecting and identifying specific antibodies in immunized animals; and applied it in a few cases to man.

Wassermann conceived the idea of applying this principle to the diagnosis of syphilis. As an antigen he substituted for the bacterial emulsion an aqueous extract of the liver of a syphilitic fetus. He found that the addition of a small amount of such an extract to the inactivated serum of a syphilitic patient, to which free complement had been added, would fix the complement present. If sensitized red corpuscles were added, no hæmolysis would occur. If a normal or non-syphilitic serum were used, the complement would remain free, and the corpuscles would be dissolved. He tested the reaction on infected apes, and also clinically on man, and obtained results so constant as to give promise of great practical value.

Subsequent work by a great many investigators has confirmed his views as to its clinical value, non-syphilitic sera rarely giving a positive reaction. But the prevailing ideas as to the nature of the reaction have been materially changed. It was soon shown by Marie and Levaditi,[3] Weil and Braun,[4] Levaditi and Yamanouchi,[5] and others that in larger quantities, extracts of normal human livers, human or guinea-pig hearts, and of some other tissues, would also fix complement when combined with syphilitic sera. The antigenic substances in the syphilitic liver extracts could not be specific, in the strict sense, not being derived from the syphilitic organism or its by-products in the affected organs, but were substances present in normal organs, occurring in the syphilitic organs in increased amounts.

It was then shown by Landsteiner, Mueller and Pötzel[6] that an alcoholic liver extract was (nearly) as efficient an antigen as an aqueous extract. Such an extract contains no complex albuminous substances such as had been supposed were concerned in the reaction, but relatively simple fatty substances known as lipoids, such as lecithin, cholesterin, and sodium oleate. It has since been shown that lecithin, and some of the others, in solution will fix complement when combined with syphilitic sera. The reaction cannot be considered biologically specific, in the sense of a combination between a specific bacterial substance and an immune body, but merely as one that has been shown empirically to be characteristic of syphilis. The exact mechanism of the reaction is not understood, but it can hardly be a specific immunity reaction, as was originally supposed.

The technique of the reaction is somewhat complicated.[7 8 9] None of the simplified methods that have been sufficiently tested have proved as reliable as the original method, which was employed in the present series, except that in most cases one-fourth of the quantity of each constituent was used.

The blood of the patient was obtained as a rule, from the median basilic vein, with a small aspirating syringe. If carefully done with a small, sharp needle, it causes practically no discomfort, and is entirely without danger. The test was usually made the day the blood was obtained; in some cases on the following day. If the serum is sterile, and kept on ice, there does not seem to be much weakening of the reaction within a week. Serum that is visibly contaminated is unfit for use. After the serum has separated, it is inactivated by heating it in a small sealed tube, in a water bath, to 56° C. for 20 minutes. This not only destroys the complement present, but also weakens the reacting power of the serum. This seems necessary, as positive reactions have been reported in non-syphilitic sera which had not been heated.[10 11] This has been confirmed in the present series of cases, several of which gave negative reactions after inactivation, but showed strong, or even complete fixation of complement when fresh. In a few cases the reverse is true, probably on account of the additional complement present in the patient's serum.

As antigen was used an alcoholic extract of a syphilitic fetal liver, in which the presence of spirochætæ had been demonstrated in sections by Levaditi's method. Where quantitative comparative tests have been made with different antigens, it has been shown [12 13 14] that syphilitic liver extracts are most satisfactory. They give positive reactions with syphilitic sera in greater dilution, and have less independent anti-complementary power, measured by the amount of extract which will inhibit hæmolysis, in the absence of any patient's serum. The activity of such extracts is quite independent of the occurrence or number of spirochætæ present. The best substitute is an alcoholic extract of normal human or guinea-pig heart muscle. Lecithin solutions are least satisfactory. Aqueous extracts of syphilitic fetal livers are more efficient than alcoholic in giving a somewhat larger percentage of positive reactions with syphilitic sera; but they are more variable, and much more unstable. The extract is made by grinding up the liver, shaking it for several hours with ten volumes of absolute alcohol, and filtering. It will keep indefinitely.

There is considerable variation in the behavior of different extracts to syphilitic sera of weak reacting power. Such sera may give a positive reaction with one extract, and a negative with another. Properly controlled, fixation with any extract that is known to be reliable may be accepted as a positive reaction.

As complement, fresh guinea-pig serum is used in 1 to 10 dilution. It was used 12 to 18 hours after bleeding. Small amounts may be aspirated directly from the heart, without injury to the animal if this be done under ether.

As a hæmolytic serum is used the serum of a rabbit immunized to sheep corpuscles. The rabbit is given intraperitoneal injections of washed corpuscles at 5-day intervals, in doses increasing from 2 to 10 cc. After 6 doses the animal is left for 10 days without further treatment. A small amount of blood is then withdrawn and tested. If active in a dilution of 1 to 1000 or higher, it is best to bleed the anesthetized rabbit to death. The serum is put in sealed tubes, inactivated and kept on ice. Thus preserved, it will lose but little strength within 3 or 4 months. In the living animal, the strength of the serum varies greatly from day to day.

The sheep's blood is obtained by aspiration from the jugular vein. It is mixed at once with 1.5 per cent sodium citrate in .85 per cent salt solution to prevent clotting. The corpuscles are removed by centrifugalization, are washed four times in salt solution to remove all trace of sheep serum, are centrifugalized to constant volume, and a 5 per cent suspension is made in salt solution.

The smallest quantity of rabbit serum that is necessary to dissolve 1 cc. of a 5 per cent suspension of sheep corpuscles in the presence of 0.1 cc. fresh guinea-pig serum is determined, and three times this amount is used in the final tests.

To 0.2 cc. of inactivated patient's serum are added 0.1 cc. guinea-pig serum, as complement, and 0.1 cc. of liver extract, each fraction being first diluted up to 1 cc. The mixture is placed in the thermostat 1 hour to enable complement fixation to occur. There is then added 1 cc. of diluted rabbit serum, the strength of which has been previously determined; and 1 cc. of a 5 per cent suspension of sheep corpuscles. The mixture is again placed in the thermostat for 2 hours, shaking gently several times during the incubation. The tubes are kept on ice over night and then read. In positive cases, where complement fixation has occurred, the corpuscles are not dissolved. In the negative cases they are completely dissolved.

Each step in the process must be carefully controlled. The serum of each patient, as well as the liver extract must be tested independently in double the quantity used in the final test, without giving any fixation of complement. The serum of a normal or non-syphilitic case must always be tested as a control, and must show complete hæmolysis. Partial fixation may be considered as indicating a positive reaction, provided the degree of hæmolysis is slight, and all the control tubes show complete hæmolysis. Border line cases occur where the result is in doubt. Such cases should be repeated, using if possible a different antigen solution.

Although there is nothing in the test that is technically difficult, or that requires any special skill, some experience and a uniform technique are required to insure reliable and comparable results. For example, even the manner and rapidity with which an alcoholic antigen solution is diluted may influence the result of the reaction.[11] The reliability of the results depends chiefly on the care with which each step in the process is carried out.

Aside from the difficulties in technique, there is one inherent defect in the test that has been especially emphasized by Noguchi.[15] Normal human serum contains amboceptors (hæmolysin) for sheep corpuscles, in amounts varying from a mere trace up to several times the quantity needed for the test. Hence if, in a given case, the human serum to be tested is strongly hæmolytic, the addition of the usual 2 or 3 units of hæmolytic rabbit serum may result in a large excess of hæmolysin being present. This may cause complete hæmolysis in positive cases where a small amount of complement remains free, or may even to some extent liberate complement which has been fixed. Hence a few positive reactions will be missed. An attempt was made by Bauer [16] to avoid this difficulty, but no better results were obtained than by the original method.

Noguchi has recently [15] proposed a new method which not only attempts to overcome this difficulty, but greatly simplifies the technique of the reaction. He uses the serum of a rabbit that is immunized to human corpuscles. Human serum, at the degree of dilution used in the test, does not contain hæmolysin, in any appreciable amount, for human corpuscles. He also thinks it unnecessary to inactivate the sera. He reports a larger percentage of positive reactions in certain and doubtful cases than by the original method, and in cases in which this was negative, showed that the serum in question contained an excess of amboceptors for sheep cor-

pusces. He has tried to make it more generally applicable by drying on bits of filter paper the antigen solution and the hæmolytic serum, each in quantities suitable for a single test. It promises to be a very important and practical simplification of the reaction. In a limited number of cases in which it was tried here, using papers very kindly furnished by Noguchi, fairly satisfactory results were obtained.

The results that have been reported are about as follows:[7 17] In primary syphilis from 50 to 60 per cent give a positive reaction. In active secondary and tertiary syphilis, 80 per cent or more are positive. In latent syphilis about 40 per cent are positive. In congenital syphilis[18] 90 to 100 per cent are positive.

Cases of tabes and general paresis also give a positive reaction, both in the spinal fluid and the blood serum; tabes in 50 to 60 per cent; general paresis in 90 to 100 per cent.[17 18 19 20] Patients giving no history of syphilis seem nearly as likely to give a positive reaction as those who admit an infection. The smaller percentage in tabes is possibly to be attributed to the slower course of the disease, and the longer interval since the syphilitic infection. In view of the nonspecificity of the reaction, it can hardly be accepted as final proof of the pre-existence of syphilis in all such cases.

A few conditions have been reported giving a positive reaction where syphilis could apparently be excluded. The most important one is scarlet fever.[18 21] During the fever and for a few weeks after it a positive reaction is not infrequent. Positive reactions have been reported in a number of cases of leprosy,[22] in framboesia,[23] and in animals infected with trypanosomes. Isolated cases have been reported in a variety of other conditions,[24] but are so exceptional as to be open to suspicion, and detract nothing from the reliability of the reaction.

The results obtained in this clinic are quite in harmony with those reported elsewhere. No effort has been made to include many cases of manifest syphilis, but rather to select cases where the diagnosis was in doubt. The reaction was also tried in a variety of other conditions in which syphilis could be excluded.

Out of 268 cases in this series which have been studied, which Professor Barker has kindly permitted me to publish, in 99 there was nothing in the history, symptoms, or physical signs to suggest syphilis. All gave negative reactions. Some were normal or nearly normal persons. Most of them, however, were patients with serious acute or chronic disease. Among them may be mentioned: acute and chronic urethritis, pneumonia (6 cases), typhoid fever (5 cases), pulmonary tuberculosis (3 cases), miliary tuberculosis (2 cases), tuberculous meningitis (5 cases), chronic osteomyelitis, acute rheumatic fever with endocarditis, arteriosclerosis, myocarditis, and chronic nephritis (7 cases), diabetes (2 cases), arthritis deformans, advanced carcinoma (9 cases), alcoholic cirrhosis (5 cases), hæmochromatosis, Hodgkin's disease, pernicious anæmia, congenital icterus, peripheral neuritis, multiple sclerosis (3 cases), progressive central muscular atrophy, syringomyelia (2 cases), paralysis agitans (4 cases).

Of 45 cases clinically syphilitic, 33, or 73 per cent gave positive reactions. Of 5 cases of primary syphilis, 4, or 80 per cent were positive. Of 13 cases of secondary syphilis, 9, or 70 per cent were positive. Three of the 4 negative cases had received thorough treatment. Of 19 cases of tertiary syphilis with definite lesions, 16, or 84 per cent were positive.

Two of these patients showed tumors of the chest wall, clinically somewhat resembling sarcomata. In each the result of the (positive) reaction was confirmed by an exploratory incision and microscopical examination. A third patient with pulmonary tuberculosis had an ulcer on the back of the forearm of a year's duration, which for a time was believed to be tuberculous. Although he denied syphilis, suspicion as to its character finally arose. He gave a positive reaction. The ulcer healed rapidly under antisyphilitic treatment.

Of 101 cases in which the diagnosis was in doubt, 37 gave a positive reaction. In 50 of these cases clinically syphilis seems probable. Positive reactions were obtained in 33, or 66 per cent. In 51 cases in which without the reaction, syphilis would seem unlikely, 4 gave positive reactions. In none could syphilis be excluded.

Positive reactions were obtained in 2 other cases giving no history of syphilis, and presenting as their chief sign of infection a well marked general glandular enlargement.

In the series, 34 cases were found who gave a definite history of an old syphilis that could be accurately dated, varying from 4 to 45 years before examination. In 13 of these there was nothing definite to indicate an active process. Of the 13, 10 gave a negative reaction. The interval between the infection and the examination varied from 11 to 45 years, and averaged 24 years. A positive reaction was obtained in 3. One, a man of 35, was suffering from adherent pericardium, with broken compensation. He gave a definite history of syphilis 16 years before, but showed no signs of the disease except a few old scars on the shins. A second case, a man of 40, with amœbic dysentery, gave a history of infection 15 years before. He showed the scar of the primary lesion, and a slight general glandular enlargement. The third case was a colored sailor of 26, with acute lobar pneumonia. He had a primary lesion at 20. He also showed a scar, and a general glandular enlargement.

Of the 21 cases showing some sign of active disease, positive reactions were obtained in 12, and negative in 9. Of the 9 negative cases, 5 were tabetics, who gave a history of infection from 8 to 26 years before. One with an aortic aneurysm was infected 30 years before; 1 with a rectal stricture 33 years before; 1 with tertiary ulcers, 7 years before; 1 with cerebral symptoms 4 years before. Of the 12 active cases giving positive reactions, 3 were cases of tabes whose infection dated back 9, 10 and 30 years respectively. Three were cases of aortic aneurysm, 2 of aortic insufficiency, and 4 of tertiary syphilis with gummata. The interval since infection varied from 8 to 39 years, and averaged 19 years. Only 1 had had symptoms referable to syphilis in the interval.

Of special interest are the cases with vascular lesions. Of 20 cases of aortic aneurysm tested, 10, or 50 per cent,

gave positive reactions. Only 4 of the 10 gave a history of syphilis. Two of the others who gave positive reactions came to autopsy, and showed a localized productive mesaortitis, such as is usually considered characteristic of syphilis. In 9 other cases showing arteriosclerosis and aortic insufficiency, but no indications of aneurysm, 6 gave positive reactions. Only 3 of the 6 gave a history of syphilis.

In 6 cases giving clinical signs of cerebral syphilis, 3 positive reactions were obtained. One of the negative cases had received thorough treatment.

Among other cases in which the reaction was of importance in reaching a diagnosis may be mentioned a case of syphilitic cirrhosis; a case of bilateral synovitis of the knees with no other definite signs; a case of tumor of the spleen; and a case of obliterative endarteritis with gangrene of the leg.

It must be borne in mind that syphilis may coexist with other diseases. Thus, a colored man, 29 years old, came into the hospital with signs of intracranial tumor. He gave a suspicious history, and physical signs pointed to syphilis, which was confirmed by a positive reaction. At operation it was found that his serious symptoms were not due to syphilis, but to a cerebral abscess containing streptococci.

Of 15 cases of tabes tested, 6, or 40 per cent, gave a positive reaction. Of the 9 negative cases, 4 had recently received vigorous mercurial treatment. Eleven of the 15 gave a history of syphilis, and 5 of these gave positive reactions. Of the 4 who denied infection, 1 gave a positive reaction. In 5 the reaction was tested in both blood and spinal fluid. In 2 negative reactions were obtained in both; in 1, positive in both. In 1 the blood was positive and the spinal fluid negative. In 1, the spinal fluid only was positive.

In 7 cases of general paresis, positive reactions were obtained in all. All but 1 of these patients gave a history of syphilis. In 4 cases both blood and spinal fluid were positive, the blood giving the reaction in a higher dilution than the spinal fluid. In 2 the blood only was positive. In 1 the blood gave a negative reaction, but the spinal fluid a positive. I am indebted for these specimens to the staff of the Sheppard and Enoch Pratt Hospital, who kindly placed them at my disposal.

Mercurial treatment tends to weaken the reaction. But disappearance of the reaction does not mean cure. Such cases are still liable to relapse, although much less so than those cases in which a positive reaction persists in spite of treatment.[3] A positive reaction is considered by many as in itself an indication for treatment. But it is not certain that this is always the case. Instances have been cited of positive reactions in patients some years after all signs and symptoms had apparently disappeared. Such cases would have to be followed for a very long period before the presence of some latent lesion, of a developing aneurysm, or parasyphilitic affection could be excluded.

The reaction is unreliable for prognostic purposes. Mild cases yielding readily to treatment may react as strongly as severe, intractable ones. The reverse, however, is undoubtedly the rule.

In estimating the diagnostic value of the reaction, it must constantly be borne in mind that very little reliance can be placed in a negative reaction. Not infrequently a negative reaction is obtained in a patient with active secondary or tertiary lesions. In this respect its limitations are analogous to those of the Widal reaction in typhoid fever.

It is safest to regard a positive reaction as simply indicating a pre-existing infection. Though usually an active one, it may be latent, and not the cause of the symptoms present. While it may be going too far to accept a positive reaction as absolute proof of syphilis, if the exceptions noted are kept in mind, it may be considered conclusive for all practical purposes. In view of the extensive, almost unanimous confirmation it has received, the test must be regarded as a clinical method of very great reliability.

Summary.

In 99 cases where syphilis could be excluded the reaction was negative in all. In 51 doubtful cases in which clinically syphilis was not probable, the reaction was positive in 4; in 50 in which syphilis was probable, a positive reaction was obtained in 33, or 66 per cent. In 45 cases which were certainly syphilitic, a positive reaction was obtained in 33, or 73 per cent. Excluding cases which had recently received thorough mercurial treatment, positive reactions were obtained in about 82 per cent of the cases showing active syphilitic lesions. Positive reactions were obtained in 40 per cent of 15 cases of tabes, and in all of the 7 cases of general paresis which were tested.

Note.—Since the paper was submitted for publication several reports have appeared which in the main support Noguchi's claims as to the reliability of his method. However, until it has been more thoroughly controlled by experienced workers in other laboratories, results obtained with it should still be accepted with some caution, especially if the sera tested are not inactivated. It will certainly not yield reliable results in inexperienced hands.

The more recent work also indicates that the reaction affords a valuable (though not absolute) indication for treatment. With few exceptions, every patient giving a positive reaction should receive treatment with mercury until the reaction becomes permanently negative.

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ETIOLOGY OF MOVABLE KIDNEY.

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It is surprising that a condition so common and so easy of detection as movable kidney should have been for so long absolutely unknown. Nowhere in the references to Hippocrates, Galen, Paul of Aegina, or Avicenna do we find anything to indicate that they were acquainted with this abnormality. Many of the renal affections were recognized by the older writers and treated in a manner which seems rational to us to-day. Hydronephrosis, so frequently the result of a movable kidney, was described by Galen under the term Ischuria. But to Franciscus de Pedemontio, who lived the latter part of the fifteenth century, must be given the credit of being the first to call attention to the simple, uncomplicated movable kidney. Apparently, he did not lay much stress upon his discovery, and regarded it merely as an interesting anatomical curiosity with little or no clinical importance.

Not until the time of Riolan, in the middle of the seventeenth century, do we find any description of the clinical manifestations of movable kidney, known then as "dislocation of the kidney." Riolan (Encheiridium anatomicum et pethologicum, Lugd. Batav., 1649) has expressed so clearly and unmistakably his views of movable kidney that I would quote from him the following description:

Although the kidneys are firmly attached to the loins by the glue of the fat, yet sometimes they become loose and fall forwards; sometimes they slip down to the hypogastrium—not without danger to life; this is so true that it is by no means to be doubted. This happens especially, not only because of the fat in which they are wrapped liquefying, but also from their weight, when they are so large, from tumor or stone enclosed in their cavities that they cannot be held by their own fastenings in their own places, and then, for a while, they stop there, but at length rot and suffer an abscess.

Even to-day, the absorption of the fat in the capsule of the kidney is considered an important etiological factor in nephroptosis.

For a century after Riolan's publication the medical profession made absolutely no advance in its knowledge of malposition of the kidney. The great Haller, who lived during the latter part of the eighteenth century, apparently did not know any more about movable kidney than was known by Riolan.

An abstract from the posthumous works of Matthew Baillie, the last of the celebrated holders of the gold-headed cane, indicates how much was known in regard to nephroptosis at the beginning of the nineteenth century. Baillie says:

In four or five instances I have felt a loose tumor in the situation of one of the kidneys, which could easily be moved up and down with slight pressure from the hand. The tumor is of considerable firmness, and has a good deal the shape and size of the kidney. It is attended with very little uneasiness to the patient, and the general health is very little, if at all, affected by it. When felt in women it has been mistaken for an enlarged ovarium; but it has neither the shape of an enlarged ovarium, nor is it in the situation in which an enlarged ovarium is commonly found. I have not had an opportunity of examining this

disease in the dead body; I am therefore not certain about its nature, but I am rather disposed to think that it is a kidney more loosely attached than usual to the subjacent and surrounding parts.

In the Lancet, of 1836, there appeared an article by R. C. King describing an operation, which, although unsuccessful, was so far as I can discover the first attempt to cure a movable kidney by surgical means. King says as follows:

In March, 1834, Sophia Puttock, aged 40, complained of suffering very greatly from a variety of unpleasant feelings in her abdomen, back, and lower extremities. She spoke of herself as being rendered perfectly miserable and feeling her life a burden. On examining the abdomen, I perceived a tumor situated on the right side, about midway between the superior spine of the ileum and the edge of the ribs above it: the tumor appeared to be between 4 and 5 inches long, and 2 or 3 inches broad, forming in shape more or less of the segment of an ovai. It was tender to the touch, and apparently attached by an extended medium. It could be moved with facility in all directions downward, and laterally, to an extent of 4 inches. It could be passed upwards in the direction of the liver until it seemed to disappear under its concavity; and when it was pressed upon in that direction it became lost to the touch, and did not descend without an alteration in the position of the person, but whenever an examination took place, in the first instance the tumor was always in its centrical position. I cannot say that I thought that the health of the person was particularly deranged, or much affected by the presence of the tumor, but there was a depression of feeling which rendered life so irksome as to create a disposition to submit to any treatment which might afford a prospect of relief. All the usual modes of treatment having been resorted to without benefit, I asked the patient if she was willing to have it removed. She embraced the suggestion with eagerness, and pressed me so much to make the attempt that I consented. Indeed, the night before the day fixed for the operation, she wrote to me, expressing a hope that I should not waver in my resolution, as her own determination was not in the least shaken. The case was examined by my friend, Mr. Jeaffreson, surgeon, of Framlingham, and he coincided in the opinion that an attempt to remove the tumor was justifiable, under existing circumstances. On the seventh of March, 1834, the operation took place in the presence of Mr. Jeaffreson, Mr. Lanchester, of Laxfield, and five other members of the profession. Previous to its performance they were asked, seriatim, to examine the patient, and give their opinions of the propriety of the attempt. They all agreed that the attempt was justifiable.

The patient was laid in a horizontal position, and a vertical incision was made through the parietes of the abdomen and linea semilunaris, to the extent of about 7 or 8 inches. On the cavity being thus exposed, the fingers were passed down to search for the tumor; it was not met with. To give greater facility for examination, the wound was enlarged in the direction of the lumbar vertebræ, for about 4 inches. The search was repeated most carefully, not only in the perpendicular direction, but upwards towards the liver and the small of the stomach. Several of the gentlemen present repeated the attempt to find the tumor, but unsuccessfully. The kidney of the same side was handled, and appeared to be more movable than natural, as it could be raised from its position nearly 2 inches. After the cavity of the abdomen had been exposed for about 20 minutes, it was determined to reclose it, which was done without difficulty, by the common interrupted suture.

The description of this operation by King would seem to indicate that the medical profession at that time was still a little hazy about the symptoms of movable kidney. It was, however, only seven years later (1841) when appeared that excellent work by Rayer, entitled "Traité des maladies des reins." I am sorry that time does not permit me to quote extensively from the work of Rayer, but I will at least give his views concerning the etiology of movable kidney, as it has a direct bearing upon the trend of this paper, and also coincides pretty well with the generally accepted views of the present day.

Rayer says:

The mobility of the kidneys constitutes a morbid state which has been little studied and which is much more frequent than is commonly thought. The right kidney is almost exclusively the seat of that anomaly; it is more frequent in women than in men. Often it occurs with an increase in the size of the liver, with a displacement of the intestine, or with a displacement of the uterus; it may also be the result of a particular arrangement of the peritoneum, from a deviation of the kidney, from a twisting of the vessels, etc. Multiple pregnancies, efforts to carry or to lift heavy objects, have appeared in some cases to be the cause of displacement of the right kidney, which in other cases could not be explained.

Since the time of Rayer, the literature which has accumulated upon all phases of movable kidney is tremendous, and I shall not attempt to review it in this paper. There have appeared, however, two monographs which especially interested me and which are directly responsible for the few investigations which I have made. The first, by Becher and Lenhoff, entitled, "Körperform und Lage der Nieren," appeared in the Deutsche medicinische Wochenschrift of August, 1898. The other by H. L. Harris, entitled "Movable Kidney—Its Cause and Treatment," appeared in the Journal of the American Medical Association, June 1, 1901. Becher and Lenhoff were impressed by the fact that the patients having movable or floating kidneys also had a fairly distinct type of chest and abdomen. The chest which they associated with movable kidney was long, narrow, and contracted at its lower end; or in other words, funnel-shaped, in contradistinction to the broad, cylindrical, well-developed chest. In 1901, Harris after examining a large number of cases came to the same conclusion as Becher and Lenhoff that the shape of the chest was the chief etiological factor of nephroptosis. The conclusions of Becher and Lenhoff and of Harris seemed to be so well founded that I was surprised to find that in the numerous articles appearing since 1901, very little reference was made to their work.

The deductions which I shall draw later are based upon the routine examination of 103 white women, 50 colored women, and 25 white men.

In each case I noted the age; occupation; any loss of weight, with cause; clothing, such as history of lacing, etc.; any previous injury; general appearance of the patient, whether well-nourished or emaciated; the condition of the abdominal wall, whether fat or thin, tense or relaxed; also examination of the pelvic structures; and finally, the following measurements: The distance from the suprasternal notch to the top of the symphysis pubis, circumference of the

lower part of the chest at the level of the seventh costal cartilage, circumference of the abdomen at the level of the umbilicus, circumference about the crest of the ilium, size of subcostal angle, and the distance from the crest of the ilium to the last rib. The measurements were taken with the patient flat on the back with no pillow under the head. The circular measurements were also taken at the end of normal expiration. The patients were always examined in both the supine and standing positions. By far the best method to detect a movable kidney is with the patient standing. To examine the right kidney, have her rest the right foot on some object about six inches high and lean a little to the right side. For the left kidney a corresponding position is assumed. This gives maximum muscular relaxation and full play to gravity.

I have not considered a kidney abnormally mobile unless half or more of the organ could be felt. In most cases if thorough relaxation is obtained and the patient is not too fat, the lower pole of the right kidney can be felt, so that it can hardly be considered abnormal.

The routine examination of seventy-five unselected cases of white women revealed movable kidney in sixteen, or 21.3 per cent. In some, only half of the kidney could be felt, while in others it could be displaced to the pelvis and opposite side of the abdomen. In fifty colored women there were four cases of movable kidney, or 8 per cent. Examination of twenty-five white men revealed only one movable kidney, or 4 per cent.

Nearly all of these women were patients in the gynecological dispensary, so that possibly the same number examined elsewhere might show somewhat different results. At the same time, I have examined on the wards and elsewhere thirty-four cases of movable or floating kidney, making in all, fifty cases. This would not be a very large number from which to draw conclusions, except for the fact that during the past three years, I have examined for movable kidney most of the patients that have fallen to my lot—between two and three thousand. And I find that the results gotten by examining carefully a smaller number of patients agree fairly accurately with results obtained by superficial examination of over two thousand cases.

Let us first consider briefly some of the generally accepted causes of movable kidney.

Pregnancy.—As movable kidney is so much more frequent in women than in men, it is natural when seeking a cause, that those functions peculiar to women should be considered of great etiological importance; and pregnancy, the function which causes such changes in the relation of the abdomen and pelvic viscera, was among the first to be held responsible for nephroptosis.

Landau, of Berlin, in 1881, made the following statement:

> The vast majority of women affected with movable kidney have borne many children, and, as shown by the appended table of my own observations, it is striking how frequently their deliveries had followed each other closely. Among the 42 cases observed by me only two are nulliparæ, and of these, one had carried a large ovarian tumor for 18 years and had acquired a pendulous belly after I had removed it.

It is hard to understand how Landau could have gathered such remarkable statistics, for we know now that movable kidney is quite common in nulliparæ.

The fifty cases of movable kidney which I recently examined showed the following results:

1	had	had	12	children.
1	"	"	10	"
1	"	"	9	"
2	"	"	8	"
1	"	"	7	"
1	"	"	6	"
3	"	"	5	"
2	"	"	4	"
4	"	"	3	"
11	"	"	2	"
7	"	"	1	child.
15	"	"	0	children.

An average of 3.5 children for each parous woman, with 30 per cent nulliparæ. And 66⅔ per cent had not had over two children. Only four had been delivered instrumentally.

On the other hand, an analysis of the cases which did not have movable kidney showed that

1	had	had	11	children.
1	"	"	10	"
2	"	"	9	"
1	"	"	7	"
2	"	"	6	"
2	"	"	5	"
6	"	"	4	"
4	"	"	3	"
2	"	"	2	"
19	"	"	1	child.
19	"	"	0	children.

Thus an average for the parous women of 3.2 children, while the nulliparæ composed 32.2 per cent. But there were fifteen cases that had been delivered instrumentally.

Our statistics also show that movable kidney in a colored woman is uncommon, yet an analysis of their pregnancies show the following:

4	had	had	7	children.
1	"	"	6	"
2	"	"	5	"
2	"	"	4	"
2	"	"	3	"
6	"	"	2	"
13	"	"	1	child.
20	"	"	0	children.

An average of 2.8 children for each parous woman, with 20 per cent nulliparæ.

To recapitulate, the nulliparæ composed 30 per cent of the cases of movable kidney, 32 per cent of the cases without movable kidney, and only 20 per cent of the colored women, in whom movable kidney is uncommon.

I believe in many instances, pregnancy and parturition play an accessory part in the causation of movable kidney,

but it is not, as so generally assumed, of such great etiological significance.

Ascites, abdominal tumors, and other pathological conditions causing increased intra-abdominal pressure, may possibly in isolated cases, cause a dislocation of the kidney. But when we consider that nephroptosis occurs in over 20 per cent of adult white women, and that these pathological conditions do not affect 1 per cent of women, it is evident at a glance that they are of no very great significance.

Chronic Constipation.—Some observers, notably Longyear of Detroit, have emphasized constipation as an etiological factor of nephroptosis, especially of the right side. Longyear (American Journal of Obstetrics, Vol. LIV, No. 5) describes bands which he calls the nephrocolic ligaments extending between the large bowel and kidneys, by means of which the latter are dragged down. He says as follows:

> The nephrocolic ligament is formed by an aggregation of fine fasciculi, originating in and being identical with the fibrous tissue forming the framework of the fatty capsule of the kidney, which, after enveloping the kidney in a fine network, passes downward and is inserted into the posterior wall of the ascending colon on the right side, and the descending colon on the left side. Its structure, as well as its action, may be compared to that of a network covering a balloon, the cords of which extend downward and support the car. The kidney is the balloon and the cecum the car. The kidney descends or not, according to the laxity of its supports and the degree of traction exerted on it by the cecum. The cecum consisting of a sac with its outlet upward, the contents of the viscus must be always forced in that direction, which necessitates the application of tractile force in the opposite direction, and as the nephrocolic ligament is a firm and unyielding attachment, the kidney is pulled downward.

He also states that floating kidney is fifteen times more frequent on the right side than on the left.

This theory sounds attractive, but we find the following objections. In the first place, the difference in frequency between the right and left sides is not so great. We found the right kidney prolapsed forty-five times and the left twenty-three times, or a proportion of two to one. In seventeen cases both kidneys were prolapsed in the same patient. Also, in the first hundred and sixty-five nephrorrhaphies in the gynecological service of this hospital, one hundred and twenty-seven were on the right side and thirty-eight on the left, or a proportion of three and a third to one. In ten cases both kidneys were suspended in the same patient. So that Longyear's estimate of fifteen floating right kidneys to one left kidney would seem, both from our dispensary and operative statistics, to be out of all proportion, and that three to one would be more nearly correct. In the second place, a history of constipation was obtained in 49 per cent of white women and in 70 per cent of colored women; or, in other words, white women in whom movable kidney is common do not suffer from constipation as frequently as do colored women in whom movable kidney is uncommon.

Longyear uses this nephrocolic ligament to suspend the kidney, and he has stated his successes and failures so candidly that his work deserves attention; but if this nephrocolic ligament plays an important etiological part in nephroptosis, it must be an anatomical structure peculiarly developed in white women and not in men or colored women, and that is not probable.

Corsets, abdominal bands, and other articles of clothing have been held responsible for nephroptosis. It is very difficult to obtain accurate statistics upon this point, for what one woman considers tight lacing, another would consider only moderate. Becher and Lenhoff examined South Sea Islanders, with whom clothing is an unknown luxury, and found movable kidney just about as often as in civilized races, showing conclusively how small a part clothing plays.

Wolkoff and Deletzine from post-mortem examinations ascribed the preponderance of movable kidney in women to the shape of the renal fossæ. They claimed that in men the niches in which the kidneys lie are rather deep and wider above than below, that is, funnel-shaped; while in women they tend to be cylindrical and wider below, especially on the right side. This seems to be of considerable importance in some cases, for during the operation for suspension of the kidney, it is frequently noticed that the renal fossa is very shallow and occasionally almost absent. As movable kidney is uncommon in colored women, further study upon the shape of their renal fossæ would be interesting and instructive.

As the kidney is held in position chiefly by its capsules, it is possible that a rapid absorption of the fat about the kidney would tend to cause a prolapse. In our series we have been able to obtain a history of acute illness with loss of weight in only a small percentage of cases.

In a recent work, entitled "Movable Kidney a Cause of Insanity, Headache," etc., Suckling has devoted over half of the chapter on etiology to an enumeration of individual cases of nephroptosis following severe injury. I grant that occasionally a blow or fall may cause a descensus of the kidney, but I believe nearly all the cases so classed are due to some other factor, the injury simply attracting attention to a preexisting nephroptosis. Constantly heavy lifting or repeated injury do aggravate a beginning nephroptosis, if there be present the peculiar shape of chest, of which I shall speak later.

If any of the cases of nephroptosis were attributable to gynecological trouble we should certainly expect to find them in a gynecological dispensary. As a matter of fact, in fifty cases, malposition of the uterus was present in thirteen, relaxed vaginal outlet in six, and a small myoma in one; making at the most only twenty cases in which there could be any possible connection between the renal and pelvic conditions and the majority of these seemed to be mere coincidences; while the other thirty had either a normal pelvis or something mild, as a urethritis or salpingitis.

This brings us to the study of the relation between the shape of the chest and abdomen and movable kidney. It is apparent to the casual observer that the chests of women vary greatly. Now the type of chest associated with movable kidney is rather long, narrow, and contracted below, or fun-

nel-shaped. To simply state that a chest is broad or contracted or that an abdominal circumference is large or small, would be very vague indeed. So that I have followed somewhat the example of Becker and Lenhoff and have taken various measurements, three of which I consider cardinal. The first measurement is a vertical one from the suprasternal notch to the top of the symphysis pubis. The second measurement is a circular one at the level of the seventh costal cartilage, that is, in a plane just above the upper poles of the kidneys. The third is the circumference of the abdomen at the level of the umbilicus, which is just below the lower poles of the kidneys. Now what we desire is some means to compare the various forms of chests and abdomens. If we divide this upper circular measurement at the level of the seventh costal cartilage into the vertical measurement from the suprasternal notch to the symphysis pubis, we will obtain a quotient which will serve as an index of the amount of contraction of the chest at that level, that is, just above the upper poles of the kidneys. This we will call Index No. I. If now we divide the lower circular measurement at the level of the umbilicus into the vertical measurement, the result will be an index of the amount of contraction just below the lower poles of the kidneys. This we will call Index No. II. If we divide the lower circular into the upper circular measurement, we will obtain an index of the amount of contraction which takes place between the seventh costal cartilage and the umbilicus, or the portion of the body in which the kidneys lie. This we will call Index No. III.

We will consider first Index No. I. For example, suppose the distance from the suprasternal notch to the symphysis pubis is 48 cm. and the upper circumference is 64 cm., then dividing 64 into 48, and to avoid fractions, multiplying by 100, the result will be 75, which is Index No. I of that particular body. Now from the examination of a large number of white women, the average index is found to be 72.5. Obviously, if the lower part of the chest is contracted, that being the denominator, the index will be high, and for the same reason a broad chest will give a low index.

Now the average index of the woman without movable kidneys is 71.6. There, you see, in women without movable kidney, the index is distinctly lower. In the cases of nephroptosis, there is a relative contraction of the lower part of the chest, and we should expect the index to be high. The average of fifty cases of movable kidney was 77.9.

It has been mentioned before that movable kidney is rare in men. Now in men the chests are broad at their lower portions and the average index is 67.5. Thus, we have an ascending scale: men 67.5, women without movable kidneys 71.6, the normal 72.5, and women with movable kidneys 77.9.

In the series, there were, of course, exceptions, but there was usually some definite reason to account for each exception. For example, one woman, age fifty-five, had bilateral floating kidneys with a low index; but she also had a large emphysematous chest. Previously she may or may not have had the typical chest of floating kidney, but the development of the emphysema distorted the body measurements, so that in her case the index is of no value.

All that has been said applies to Index No. I, or the relative amount of contraction at the level of the upper poles of the kidneys. Index No. II, which we shall next consider, represents the relative contraction just below the lower poles of the kidneys. As you see, we again obtain the same results as in Index No. I, the broad chests of men with the low index as contrasted with the movable kidney chest with its high index. Although here the difference between men and women with non-movable kidneys is not so great.

Examinations of colored women show that Indices Nos. I and II run higher than in white women, and for that reason we would expect to find movable kidney at least as frequent as in white women, but on the contrary we find them much less frequently.

At first sight this would seem to invalidate all our work, but the explanation is found in Index No. III. This, as I have said before, is obtained by dividing the circumference at the umbilicus into the circumference at the seventh costal cartilage. It represents the difference in contraction between those two levels, the upper and lower poles of the kidneys. In the average white woman the upper and lower circumferences are about the same, or in other words, the area of body-cavity in which the kidneys lie is more or less cylindrical. In women with nephroptosis, the lower part of the chest is contracted, consequently the measurement at the seventh costal cartilage is less than at the umbilicus, and is represented by an index of 97.6. In men the lower part of the chest is broad, and consequently the circumference is higher than at the umbilicus, and represented by an index of 106.1.

Right here lies the explanation for colored women. Their circumference at the lower part of the chest is a little larger than at the umbilicus, and is represented by an index of 102.1. They approach the type found in men, but the index is smaller. And, as has been previously shown, movable kidney occurs less frequently in colored than in white women, but not so infrequently as in men.

We could select from our series any number of cases to corroborate this brief summary which I have given, but I have purposely refrained from doing so, for it would be very tiresome and require far more time than is allotted to me.

In conclusion, I would say that pregnancies, chronic constipation, severe injuries, and gynecological conditions, may in a very small percentage of cases, of themselves, cause nephroptosis, and that the peculiar body-shape is not a *sine quâ non*. But in the great majority of cases they are simply accessory, and the true underlying cause, more important than all other factors combined, is the typical body-shape. This may be quickly determined by the three cardinal measurements. In doubtful cases it may be of slight value in diagnosis, but it is especially useful for prognosis when selecting cases for nephrorrhaphy.*

* Elaborate statistical tables of the cases studied are omitted from lack of space.—EDITOR.

DISCUSSION OF NEPHROTOMY BY THE SILVER-WIRE METHOD, WITH A REPORT OF TWO CASES.

By Edward H. Richardson, M. D.,

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Kidney surgery is always attended with a certain degree of anxiety because of the danger of hemorrhage. Even the simpler operations upon the kidney, such as fixation or decapsulation, are not exceptions to this rule. Because these operations are usually done through small incisions with imperfect exposure of the vessels at the hilum, and the manipulations necessary for stripping off the fatty capsule or the *Capsula propria*, on the one hand, or for placing the fixation sutures, on the other, may result in rupture of an aberrant vessel, or in lacerations of the cortex that will give rise to very troublesome oozing, or indeed, even to disastrous hemorrhage. The dangers are greatly increased, of course, in operations upon extensively diseased kidneys, in which it becomes necessary to release dense perirenal adhesions, and to deliver the organ outside the body.

Various operations have been devised to lessen the dangers incident to kidney surgery, and to meet specific indications.

The prime object of them all, however, is to forestall possible catastrophe through early exposure of the trunk vessels, without too much mutilation. So that in the event of sudden unexpected hemorrhage, the operator will be master of the situation.

Thus one may approach the kidney by the transperitoneal, or the lumbar route. The line of incision may be parallel, perpendicular, or oblique to the longitudinal axis of the body; or it may be a combination of any two of these. Further, it may be a simple muscle-splitting operation without division of muscle fibers, as exemplified by the ordinary kidney fixation through the superior lumbar triangle; or it may be a complete transverse division of the lumbar and hypochondriac parietes, with resection of one or more ribs, and eversion of a large flap of chest wall, in order to expose an enormous hypernephroma, for example. Between these two extremes there are, of course, many possibilities.

There has been developed, therefore, an operative technique in renal surgery that will satisfactorily expose any condition of the kidney that is amenable to surgical treatment. But, curiously enough, this operative technique has been developed almost entirely with reference to the extrinsic renal vessels, and comparatively little attention seems to have been paid to the intrinsic vessels from a surgical standpoint.

Exploration of the kidney, or nephrotomy, is one of the commonest of all operations upon this organ. Hemorrhage is, of course, the chief source of danger; and surgeons employ various devices for its control. One of the commonest is to expose the hilum, and completely shut off the renal circulation temporarily by compression of the renal vessels. Then, at the end of the operation, by transfixing the kidney with mattress sutures of catgut, or by gauze packs, or by a combination of both, the bleeding is controlled.

Another device, used especially in the removal of stones from the kidney pelvis, is to employ specially constructed blunt instruments, or simply an ordinary artery clamp, which, when forced through the kidney tissue, will push aside the larger vessels without wounding them, and permit one to grasp the stone and withdraw it without provoking serious bleeding.

It is obvious, though, that however ingenious such devices may be, an intimate knowledge of the distribution of the intrinsic kidney vessels is of paramount importance in any method of nephrotomy. For if there are certain renal zones relatively free from vessels of any size, through which the kidney can be satisfactorily explored, familiarity with their location is certainly a valuable asset to the operator. It lessens the dangers of the operation, rids the surgeon of much annoyance, and reduces a more complex operation to the category of the simple, in that primary exposure of the vessels at the hilum is rendered unnecessary, and the simple muscle-splitting incisions may be safely employed, rather than the extensive muscle-division ones.

In 1901 Mr. Max Brödel (Johns Hopkins Hosp. Bull., Vol. XII, Jan., 1901) published the results of his elaborate and pains-taking injection experiments on a large series of human kidneys, undertaken to determine the actual form of the kidney pelvis, together with the course and distribution of the larger renal vessels.

From a surgical standpoint this was a most important contribution. It emphasized three points of very great practical value.

First, that at the hilum the renal artery divides as a rule into four or five branches so distributed with regard to the pelvis that three-fourths of the blood supply passes anteriorly, and one-fourth posteriorly. That, the arteries are end-arteries in the strictest sense, the branches of the anterior division never crossing over to the posterior side, or *vice versa*. They do not anastomose with each other.

Second, that while the veins of the two divisions anastomose with each other through two systems of arches, one of which surrounds the bases of the pyramids, while the other encircles the necks of the calyces, yet, through the latter channels, the blood is poured into the larger collecting veins at the hilum, all of which also pass anterior to the pelvis.

Finally, that there are certain surface markings of the kidney that will usually enable the surgeon to determine fairly accurately the location of the planes of arterial division.

The value of these facts in renal surgery is, of course, obvious. Viewed in the light of them nephrotomy becomes a comparatively simple and safe operation, leaving, at first sight, little to be desired as regards operative technique.

E. K. Cullen and Derge (Johns Hopkins Hosp. Bull.,

Vol. XX, Nov., 1909) have just published, however, another most important contribution to the operative technique of nephrotomy.

Basing their work upon the anatomical facts established by Brödel, they undertook two series of experiments on dogs to determine first, whether the direction of the incision in nephrotomy had any appreciable effect on the resulting hemorrhage; and second, whether the bleeding would be less if a silver wire of low tensile strength (No. III) was used instead of the knife in splitting the kidney from within outwards.

They concluded from the first series of experiments, as one would naturally expect from the tree-like branching of the arterial trunks, that the hemorrhage was definitely less when the knife was passed from pelvis to cortex than from cortex to pelvis.

The results of the second series of experiments were even more striking.

By threading the silver wire on a straight liver needle (Konsnietzoff-Cullen), it could be passed through the kidney from pole to pole, or transversely at any level desired, without wounding any vessels of moment, inasmuch as the blunt, flat needle easily pushed aside the vascular trunks lying in its course. With an assistant firmly holding the kidney to prevent undue traction on the vessels at the hilum, the organ was easily divided to any extent desired by a gentle see-saw motion of the wire, with the traction exerted in a cortical direction.

The advantages of the silver wire over the knife were most satisfactorily shown. There was always free bleeding from the cut surfaces where the knife was used, with usually some actively spurting arteries, while following the silver wire divisions, to quote the authors: "How insignificant the hemorrhage may be was well illustrated in one experiment where, after the kidney had been split from pole to pole and the pelvis opened, it was left undisturbed outside the body of the animal while the other kidney was being operated upon. Though the renal vessels at the hilum were not compressed in the least, and the kidney, pulsating synchronously with every heart-beat, was laid open like an open book, there was practically no bleeding from the cut surfaces several minutes after the incision had been made."

It is evident, as the writers go on to state, that very little suturing is necessary after nephrotomy thus performed.

Certainly this work represents a most important advance in renal surgery. It will admit of a wide field of application. It will greatly simplify many kidney operations, and it will in many cases obviate the necessity of a preliminary control of the vessels at the hilum, and thus do away with the necessity of extensive incisions with division of the muscles.

Since the silver-wire method was devised there have been only two cases in the gynecological department in which nephrotomy was indicated.

I was fortunate enough to have the opportunity of operating upon both of these cases on the same day. The silver-wire method was used in both of them, and the results obtained demonstrate conclusively two points. First, the value of the silver-wire method of nephrotomy in certain cases; and second, that the method very clearly has a limited field of application, and should not be employed in every case in which nephrotomy is indicated.

A synopsis of the cases is as follows:

CASE I.—Mrs. M. L. (Gyn. No. 15,672), age 41 years, was admitted to Johns Hopkins Hospital April 6, 1909, complaining of periodic attacks of pain in the right lumbar region.

History.—Twelve years prior to admission she had undergone an abdominal operation in Germany for extensive pelvic inflammatory disease; bilateral salpingo-oöphorectomy being done. Eight years prior to admission she was operated upon in this hospital for renal tuberculosis; a left nephro-ureterectomy being done. For three years following this operation she was treated at intervals in the out-patient department for tuberculous cystitis, which finally cleared up, the patient remaining free from symptoms for three years. The present illness began two years prior to admission with periodic sharp attacks of pain in the right kidney region, which gradually became more severe. About December, 1908, these attacks of renal colic began to recur at intervals of three to four days, with such agonizing pain that the patient was practically incapacitated. The pain was knife-like in character, and radiated along the course of the right ureter to the bladder. She had no chills or sweats with them. Nor had she observed any abnormality in the urine following any attack.

Her general condition at the time of admission last April was good, nothing of importance being discovered on careful physical examination, except slight tenderness on bimanual palpation of the right kidney; which, however, was not perceptibly enlarged, nor was it displaced. There was also considerable thickening felt on vaginal examination about the lower portion of the right ureter. The urine was acid and slightly cloudy, but repeated careful searches for tubercle bacilli gave negative results.

Under general hygienic measures, together with bladder irrigations and instillations the cystitis improved markedly during the first two and one-half months of her stay in the hospital. The attacks of renal colic continued, however, at intervals, so that after the bladder infection had greatly improved, the right ureter was catheterized with a wax-tip catheter. But no evidence of stone was found; and the capacity of the kidney pelvis was normal. The X-ray was also negative. There was, however, always an evening rise of temperature to 99.5° F. About the middle of June the attacks of renal colic became much more intense, and were associated with agonizing bladder spasms, and marked increased frequency of urination. She also had chills, with elevation of temperature to 102° F., and sweats. This condition became so distressing that on June 28 I made a vesico-vaginal fistula, in order to put the bladder at rest, and instituted continuous bladder irrigations for five hours daily.

Following this operation the attacks of renal and bladder pain entirely disappeared. The patient's general condition greatly improved, and the bladder cleared up entirely by August 10. So that on this date I operated again and closed the fistula, which healed perfectly throughout.

Eight days after this operation, however, the old pains returned again with increased severity, and the patient rapidly became seriously ill. She had constant fever of 102°-103° F., with daily chills, profuse sweats, nausea and vomiting. She took very little nourishment, and lost weight rapidly; her condition by the first week in September becoming critical.

She suffered so intensely that she begged to have the kidney explored, even after understanding fully the dangers of neph-

rotomy in her poor general condition, and with only one kidney, which was probably diseased; saying that she greatly preferred to die under the operation than to longer endure the pain.

On September 8 I exposed the kidney through the superior lumbar triangle, and after considerable difficulty, owing both to the fact that it was hypertrophied to nearly double normal size, and was also quite densely adherent about the upper pole, I succeeded in delivering it intact outside the body. Nothing abnormal could be felt either in the kidney itself, the pelvis, or the upper portion of the ureter.

I then passed a long, straight liver needle, carrying a number III silver wire, into the kidney at the lower pole close to the hilum, and out a little posterior to the mid-point of the convex border. The capsule between the two ends of the wire was then incised along the convex border, and by exerting gentle traction, with a see-saw motion of the wire, the lower half of the kidney was laid open. The needle was then re-entered in the depths of the wound and caused to emerge at a point on the upper pole corresponding to the one at which it had been introduced on the lower pole. The upper half of the kidney was then similarly divided, and the entire organ opened like a book, with the pelvis clearly exposed to view. The large size of the kidney forced us to do the bisection in two stages, because the longest available needle was too short to reach from pole to pole.

The trifling amount of bleeding from the cut surfaces of the kidney was indeed remarkable, although no compression whatever was being exerted on the vessels at the hilum. After carefully examining all parts of the kidney and its pelvis, the two halves were again brought together, and a few mattress sutures of catgut served to completely check the slight venous oozing.

Unfortunately, we found nothing whatever to account for the renal crises. There were a few scattered pin-head sized areas that looked suspiciously like tuberculosis, but no definite tubercles were seen.

Curiously enough, however, the patient was very greatly benefited by the operation. Beginning a few days afterwards she began to improve. She has had only one slight attack of pain in the past two months, has gained eight pounds in weight, and is now up and about the ward daily.

Case II.—Mrs. B. J. (Gyn. No. 16,006), age 31 years, was admitted to Johns Hopkins Hospital on September 2, 1909, complaining of chills and pain in the right side.

History.—The family and past histories are unimportant. The present illness began eight months prior to admission with pain on urination and increased frequency. No blood but much pus had been noticed in the urine. During the past month prior to admission she suffered with periodic attacks of sharp pain in the lower right abdomen. The pain did not radiate. She had chills, elevation of temperature to 104.5° F., sweats, nausea, and vomiting with the attacks, which recurred with striking regularity every day. The duration of an attack was from 1½ to 2 hours. She had lost 20 to 30 pounds in weight.

The general examination on admission showed that the patient was quite ill. She looked anemic, and had evidently lost much flesh. There were suspicious signs of an early pulmonary lesion at the left apex. The right kidney was not enlarged, but was tender on palpation. The blood examination was negative for malaria, but showed a leucocytosis of 12,000. The cystoscopic examination showed a normal bladder; clear, normal urine from the left kidney; turbid, purulent urine from the right kidney. No tubercle bacilli were found in the urine. The wax-tip catheter and X-ray were both negative, no evidence of stone in the right kidney and ureter being found.

Operation.—On September 8 I exposed the right kidney through the superior lumbar triangle, and easily delivered it outside the body without division of any muscle fibers. I could not detect any abnormality from inspection and palpation either of the kidney itself, or of the pelvis and upper portion of the ureter. I then transfixed the kidney from pole to pole with a straight liver needle, carrying a silver wire. The kidney was then opened as already described. But in this case at several stages of the bisection very considerable resistance to the passage of the silver wire was encountered, so that quite strong traction was necessary to completely divide the organ. When it was laid open the cause for this was evident. The kidney contained several small abscesses. The largest one was situated in the upper pole and measured about 2 cm. in diameter. These abscesses were surrounded by dense fibrous tissue walls, which were more resistent than the kidney parenchyma and the vessels. Consequently, strong traction on the wire was necessary to divide them, and as a result of this many more vessels were torn open than would have been the case had a knife been used, and a clean cut made from within outwards. The bleeding was also very profuse, and it became necessary to compress the vessels at the hilum to control it. A nephrectomy being indicated, the renal vessels together with the ureter were skeletonized, clamped and divided, and the kidney removed.

The patient stood the operation well, but on the second day of her convalescence, her temperature reached 104° F., and she complained of pain in the right side of her chest. Upon examination we found a small patch of pneumonia, with a friction rub easily heard over it.

Fortunately, this rapidly cleared up, and her temperature reached normal on the ninth day after operation. She then improved rapidly, and was discharged well on October 12, 1909.

From these two cases we can draw several important practical lessons. The first case is a type of by far the larger group of kidney cases in which nephrotomy is indicated; and it corroborates fully the claims made by Cullen and Derge as to the advantages of the silver-wire method.

The second case, on the other hand, clearly represents a group of cases in which the silver-wire method of nephrotomy is distinctly contraindicated for two reasons. First, whenever abscesses, fibrous tissue, or other pathological conditions in the kidney render it necessary to exert strong traction on the wire in order to bisect the organ, many vessels will be lacerated, and consequently both the damage to the kidney parenchyma and the hemorrhage will be greater than if a knife were employed. Second, the pulmonary complications in the second case following operation show conclusively the dangers of omitting compression of the vessels at the hilum, and thus permitting free renal circulation while doing a nephrotomy on an infected kidney. I feel sure that in this case an infected embolus was swept into the renal vein, thence to the vena cava, right heart, and finally lodged in the right lung, where it produced a localized pneumonia.

It must be remembered that the work of Cullen and Derge was all done on normal kidneys, and that the mechanics of the method precludes its rational application to a group of cases illustrated by our second one. In the vast majority of cases, however, by combining the silver-wire method of nephrotomy with the anatomic points established by Brödel, one obtains a most satisfactory operative technique.

In conclusion, it should be emphasized that complete longi-

tudinal bisection of the kidney is comparatively rarely indicated. The non-vascular zones are so clearly marked that one can make transverse divisions of the parenchyma and open the pelvis at almost any level desired; or one can safely combine a transverse with a longitudinal division, if it be indicated. I am inclined to think, too, that the silver wire method has a further very important field of application, and that is in partial nephrectomy, an operation now less commonly done than, I believe, will be the case within another decade.

ANTI-TYPHOID VACCINATION. THE IMMEDIATE RESULTS OF THE ADMINISTRATION OF 3600 DOSES.*

By MAJOR F. F. RUSSELL,
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The history of anti-typhoid vaccination is short and quite well-known, and it will hardly be necessary to do more than mention a few facts. In India Haffkine had obtained a considerable measure of success in the prevention of cholera by means of prophylactic inoculations, and this, in connection with the experimental work of Pfeiffer, led Sir Almroth E. Wright to take up the subject of vaccination against typhoid. Pfeiffer had informed Wright, in the course of a conversation, that it was not necessary to inoculate living cultures into animals to produce agglutinins, but that these anti-bodies could also be produced by the injection of killed typhoid bacilli. The idea apparently presented itself as feasible to both Pfeiffer and Wright that other anti-bodies, sufficient in quantity to protect against typhoid fever, would also be formed in response to the inoculation of killed typhoid bacilli into human beings, for Wright reported his first two cases of immunization in human beings in 1896,[1] and Pfeiffer and Kolle reported the result of anti-typhoid vaccination in two men later in the same year.[2] Although this paper covers only two cases it is very convincing because of the completeness of the investigation, for not only was an increase in the agglutinins found to follow a single dose of vaccin, but also a very considerable increase in the bacteriolytic power of the blood when tested according to Pfeiffer's well-known method with guinea-pigs. At this time Pfeiffer suggested the use of vaccin to limit the spread of epidemics, and its use in time of war. In January, 1897, Wright[3] made a further and more complete contribution to the subject in which he reported the results of the use of anti-typhoid vaccin in 18 people.

Although Wright was more or less indebted to both Haffkine and Pfeiffer for helpful suggestions, there is no doubt but that to him belongs the principal credit for placing prophylactic vaccination against typhoid on a practical working basis.

In 1898 he vaccinated about 4000 men of the British Indian Army,[4] and in the years from 1899 to 1902 he furnished 400,000 doses to the English troops in the Boer War. It is reported that 100,000 inoculations were made, but not very much has as yet been published about the results in South Africa, and it is improbable that we shall get any further statistics of value from that campaign. The only figures which I have been able to find[5] show that 19,000 men were immunized and that the incidence of typhoid among them was only about half as much as among the untreated, and that the death rate was diminished about two-thirds.

In the latter part of 1902 considerable opposition to the inoculations developed in the English service, and they were discontinued. A Commission[6] was appointed to investigate the whole subject, and as a result the practice was reintroduced into the service in October, 1904. In the meantime Sir A. E. Wright had severed his connection with the English Army, and the work was carried on by Colonel Leishman and his assistant, Major Harrison, of the R. A. M. C.

Many thousands of doses have been given since then, and Leishman[7] has given the results of the immunization of 5473 cases. These men all belonged to 16 regiments which had been selected for a carefully-controlled investigation on a large scale. As each of these regiments was in turn ordered to service in India, a medical officer, who had been especially trained for this particular duty, was attached. He lectured to the troops on the prevention of the disease, and called for volunteers and immunized them.

As this medical officer is always present with the regiment in all its journeys, he is able to keep careful records of all men immunized, and to care for, and to vaccinate additional volunteers and recruits from time to time as opportunity offers. From his knowledge of typhoid fever and clinical laboratory methods he is enabled to make an accurate diagnosis in all suspicious cases. By means of these precautions Colonel Leishman is able to furnish statistics which are thoroughly accurate and reliable.

TABLE.

Inoculated, 5473. Cases of typhoid fever, 21. Deaths, 2, or per 1000 inoculated cases, .36.

Non-inoculated, 6610. Cases of typhoid fever, 187. Deaths, 26, or per 1000 non-inoculated cases, 3.93.

Among 12,083 men there were 5473 inoculated, and 6610 uninoculated. Among the former there were 21 cases of typhoid with two deaths, and among the latter 187 cases and 26 deaths. Among the exposed regiments who had been inoculated with the vaccin in use at present there were 3.7 cases per 1000 against 32.8 per 1000 among the untreated. Only four out of the 21 vaccinated men who subsequently developed

*Read before the Johns Hopkins Hospital Medical Society, December 6, 1909.

typhoid had had two doses of the vaccin, and they all recovered. The other 17 had received only one dose. The observations of this group of 12,000 men covers a period of over three years, and no more perfect or convincing statistics are needed to show the value of this method of prophylaxis.

There are very few facts as yet on which we can base a statement as to the duration of the protection. The English statistics just quoted show that it will last for at least three years, and from the army point of view, if it lasts three years that is long enough, for no modern war will last as long as that. Three years will also cover the period of service of hospital internes and the training period of nurses, and by vaccinating them you can reduce the number of cases to half or even less, and such a result would justify you in insisting upon its use among people whose vocation exposes them to infection. It is of course quite illogical to conclude that the immunity ceases with the disappearance of the specific antibodies from the blood, since agglutinins, opsonins and bacteriolysins all disappear after typhoid fever in the course of a few months, as a rule, and yet the immunity lasts for many years if not for life. We may compare the evolutions of the body cells after vaccination to the evolutions of troops undergoing training during maneuvers and the real attack of typhoid fever to the battle of actual war. If the cells have been trained in organized defense and offense during the artificial immunization with harmless vaccins, they are better able to mobilize promptly and properly and to suppress the invading organisms during the incubation period. If they are not successful in completely preventing the outbreak they are at least more apt to be victorious than untrained cells which are having their first struggle with the typhoid enemy.

The results of anti-typhoid vaccination in the German Colonial Army in the Herero campaign in 1904 in Southwest Africa were also quite favorable.[7] Eight thousand men were vaccinated according to the method of Pfeiffer and Kolle, and the difference in the incidence and death rates are shown by the following table:

		Cases.	Deaths
Per thousand of strength.	Unvaccinated	98.4	12.6
" " "	Vaccinated	50.9	3.3

Roughly, there were about half as many cases and only a quarter as many deaths among the vaccinated.

The *necessity* in the army for some such procedure as vaccination, and the inadequacy of other means of prevention is shown by the very great prevalence of this disease in modern wars. In the Civil War we had 80,000 cases in the Northern Army. In the Franco-Prussian War there were 73,396 cases and 8789 deaths among the Germans; in fact 60 per cent of their total mortality was due to typhoid. During the Boer War there were 31,000 cases and 5877 deaths. In the Spanish War we had 20,730 cases and 1580 deaths among 120,000 men or one case in 5.6 men. Eighty-six per cent of all deaths were due to this disease. We have no data as yet with reference to the Manchurian War.

In the event of a war to-day there is every reason to believe that we could obtain much better results in prevention than in these wars, but the number of cases would still be large, very large, in spite of the advance of our knowledge of the epidemiology of this disease during the last ten years.

The Preparation of the Vaccin.

It has been shown by Wassermann and Strong[8] that it is not necessary to use a virulent or freshly isolated culture in making typhoid vaccins. It is necessary, however, to select a culture which has good binding powers and which will produce large quantities of anti-bodies when injected into men and animals. The culture which we use was isolated from the spleen of a fatal case many years ago. It is a typical typhoid in every way and grows luxuriantly and agglutinates well with immune serum. Its virulence has not been tested lately but it is probably quite safe to characterize it as an avirulent culture. It is grown on agar slants for 18 or 20 hours, and is then washed off in a small quantity, about 2 cc., of physiological salt solution. The agar tubes are of uniform size and sloped in a uniform way on racks built for the purpose. They are sowed with a uniform quantity of a broth suspension of a 20-hour agar growth. Every effort is made to obtain two or three hundred agar tubes with the same amount of growth. They are all looked over and any which do not come up to the standard are discarded. It has proven in practice quite a simple matter to obtain a standard 20-hour growth with substantially no variation from month to month. The emulsion is well shaken to break up clumps, and a sample is taken for a bacterial count and for tests of purity of the culture. The emulsion is then filled into large (50 cc.) tubes which are sealed in the flame of a blow-pipe. The sealed tubes are then sunk in a water bath which is furnished with an electrically-driven stirring apparatus to secure an equal temperature throughout. The bath is heated to 60° C., and the tubes are kept submerged for 75 minutes, since experiment has shown that it takes 15 minutes for a large quantity of material to reach the temperature of the bath. The bacteria are therefore killed by heating to 60° C. for one hour. We have never succeeded in killing the cultures with certainty at lower temperatures or shorter exposures than this. After the cultures are thus killed, the concentrated emulsion is diluted up to about 15 to 20 cc. for each agar slant. The quantity varies somewhat as the bacterial count serves as a check, and may indicate that a little more or a little less salt solution to the tube is necessary to give a product containing 1,000,000,000 bacteria to the cubic centimeter. Before the vaccin is put into ampullæ there is added one-quarter of 1 per cent of tricresol as a matter of safety.

The vaccin is administered to two animals at least, a mouse and a guinea-pig, before any is used on human beings. The experience with tetanus in India and plague in Manila, from contaminated vaccins, has shown that this precaution is necessary. Aërobic and anærobic tests for sterility are also made on each batch of vaccin.

The Keeping Qualities of the Vaccin.

Our oldest vaccin has now been kept in the ice-box for 15 months, and inoculations into animals and man show that it is just as effective as when first prepared.

Recent Experience with Vaccin.

The vaccination of officers and enlisted men in our army was begun in February of this year (1909), and up to the present time completed records of the vaccinations of 1400 individuals have been collected.

As the work of the first year was looked upon as merely preliminary we have attempted to collect statistics as to the immediate results in the way of local and general reactions, for it was realized that any measure like this which is purely voluntary, must not be too unpleasant, painful or disagreeable, if it is to be popular.

Each dose of vaccin is followed by a local reaction which varies very little either with the size of the dose or with the idiosyncrasy of the individual. As a rule, there is a red and tender spot about as large as the palm of the hand at the point of inoculation. This begins to appear in six to eight hours, and reaches its full development in about 12 hours, and then gradually subsides and disappears, as a rule, in 48 to 72 hours. It happens occasionally, especially in children, that there is little or no local reaction, but this is rather a rare occurrence. Occasionally the red and swollen area may be unusually large and extend from the point of inoculation to the elbow or even half way to the wrist. The excessively severe local reactions are not particularly painful, and the men are able to use the arms for light work without discomfort; and it has never been necessary to make local applications to the arms, or to put the arm into a sling. The severe local reactions subside about as quickly as the average and there are fortunately not very many of them. The local reaction extends up the arm to the axillary glands in a considerable number of instances. The lymph nodes are slightly swollen and tender on pressure, and occasionally the man will call attention to them. The symptoms referable to the glandular swelling disappears in about 24 hours and are never followed by permanent enlargement or by suppuration.

At the seat of the inoculation a small hard bullet-like nodule may persist without giving rise to any symptoms for a week or two before it subsides. No instance of the continued presence of this nodule beyond a couple of weeks has come to my knowledge, and the local reaction regardless of its severity passes away completely and leaves no scar or mark of any sort to show where the vaccination has been made.

The general reaction varies in its symptoms much more than the local. In children and in many adults it can be truly said to be absent. In its milder form it causes a transitory headache and a feeling of weariness which lasts from two or three hours to a day. Slightly more marked general reactions are evidenced by considerable headache and a decided feeling of lassitude which lasts until about noon of the following day. Occasionally there are chilly sensations without much rise of temperature. A few men have complained of nausea and a very few of diarrhœa lasting for a day or part of a day. It is rather interesting to note the way in which the men themselves describe a mild reaction. So many have now expressed themselves in the same way that it seems proper to mention it here. They say "I thought I was going to have a sore throat" or "a cold" or "an attack of the grip, but as it passed off quickly I realized that it was the effect of the vaccination."

The moderate reactions are characterized by a rise of temperature to 101° to 103° F. A few have had chills, and have had the symptoms described above in a rather more pronounced form. They constituted only a small percentage of the total.

The severe reactions are those with a temperature of 103° F. and above. Most of these men report having had a chill with more or less headache, nausea, vomiting or herpes labialis; no cases of albuminuria have been reported. We have taken especial pains to obtain full reports of all severe reactions, as it was realized from the beginning that if many occurred it would interfere greatly with carrying through the immunization of the army, and it is consequently gratifying to be able to report that very few of the vaccinations have been followed by severe reactions. We do not yet know what the conditions are which bring about the moderate and severe general reactions.

The fact that a man may already have had typhoid fever at some time in the past seems to increase the chances of a moderate or severe reaction. Up to the present (December, 1909) we have collected records of the vaccinations of 124 such cases and reference to the chart on this page will show an undoubted difference in the severity of the reactions of those who have had, and those who have not had, typhoid.

The 124 cases who had previously had typhoid were arranged in seven five-year groups in the hope that this would show how long the hypersensitiveness to typhoid lasted, but the figures are inconclusive. Apparently it lasts for 30 to 35 years, but the number of cases is quite small, and other factors, such as advancing age, may be equally important in giving a high percentage of moderate and service reactions.

TABLE.

Cases.	First Dose.				Second Dose.				Third Dose.			
	None.	Mild.	Moderate.	Severe.	None.	Mild.	Moderate.	Severe.	None.	Mild.	Moderate.	Severe.
1204. No typhoid	59.9	31.4	7.5	0.9	67.8	28.6	5.3	1.1	77.2	19.2	3.0	0.4
124. Typhoid	60.4	25.8	12.0	1.6	64.6	23.2	10.3	1.7	75.0	19.5	5.4	0.0
26 within 5 years	50.0	34.6	15.3	0.0	78.2	17.3	4.3	1.7	71.4	18.9	9.5	0.0
33 " 10 "	57.5	24.2	15.1	5.	45.1	41.9	9.6	3.2	72.7	22.7	4.5	0.0
29 " 15 "	72.4	20.6	6.8	0.	71.4	21.4	7.1	0.	84.	12.	4.	0.
9 " 20 "	55.5	33.3	11.1	0.	65.5	12.5	25.	0.	57.1	42.8	0.	0.
7 " 25 "	57.1	28.5	14.2	0.	50.	50.	0.	0.	75.	25.	0.	0.
4 " 30 "	100.	0.	0.	0.	100.	0.	0.	0.	75.	25.	0.	0.
5 " 35 "	40.	20.	20.	20.	60.	0.	20.	20.	50.	50.	0.	0.

Not every case of typhoid leaves the patient in this hypersusceptible or anaphylactic condition, and the fact that such

people give a higher percentage of severe reactions than individuals who have not been sensitized by an attack of the fever was not appreciated until a considerable number of record cards had been examined. The number of cases tabulated (124) is so large that the increased severity can hardly be a

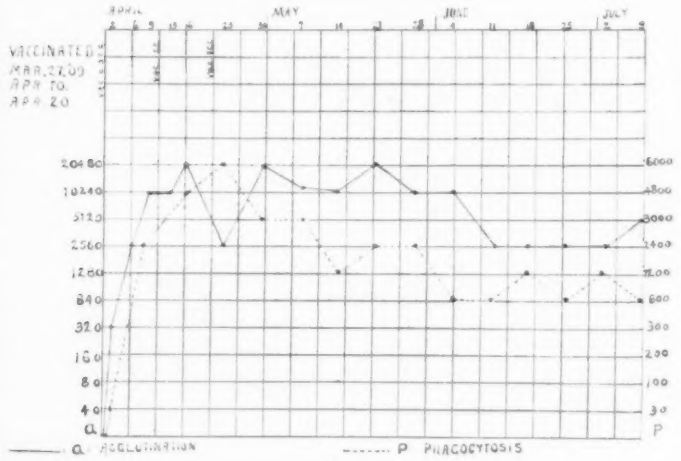


CHART I.

coincidence. Presumably it is coupled with an immunity to typhoid and it therefore is not to be classed with the hypersusceptibility of man or animals infected with tuberculosis and glanders. To what extent it may indicate residual typhoid affections of the bile tract, urinary tract or intestines, is at present unknown. Previous typhoid will not, however, explain all of the marked reactions.

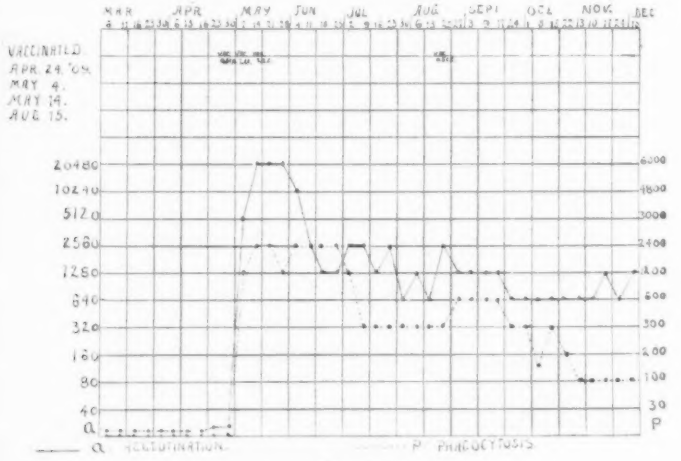


CHART II.

It is well known that the severity of typhoid varies in different epidemics, and also among individuals in a single epidemic, and one of the causes commonly assigned for this individual variation in severity is the varying susceptibility, or better, the varying resistance of the patient, and in default of any better explanation it seems reasonable to believe that the patients who show the greater susceptibility to the vaccin are those who would present the least resistance to the disease if naturally infected with the living typhoid bacillus.

Examination of the blood serum after vaccination has been made of a large number of cases and as the results are, as a rule, quite similar, the exhibition of two charts, I and II, will suffice as an example. They are neither better nor worse than many others, and are offered here merely because they cover a greater period of time and greater number of examinations than any others which we have made. The men were vaccinated in March, 1909, and weekly observations on the agglutination and on phagocytosis have been made regularly. No curve of bactericidal power is shown for we have not yet been able to get any method which will give *in vitro* altogether satisfactory results over a long period.

All agglutinations are done by the macroscopic method, and the serum dilutions are made with great care, and can be considered quite accurate. An increase in the agglutination is often evident on the fourth or fifth day, and by the sixth to eighth day a considerable increase is always noted. The curve shoots up rapidly to 1-10,000 and even to 1-20,000. The fall begins in about six weeks and continues to approach normal more or less slowly so that at the end of 15 months in my oldest case it is not evident in dilutions above 1 in 80 to 1 in 100. In exceptional cases the curve is neither so high nor so long as in the chart exhibited. The curve of phagocytosis is equally well marked. The rise is sharp and high and the titer reached is usually 1-5000. It falls more rapidly than the agglutination curve, but even after 10 months in the oldest case it has not yet dropped to normal. We encountered rather more trouble in developing a satisfactory routine technique for this test than for the agglutinations, and our observations consequently do not go so far back. The opsonic index when obtained by ordinary methods fails completely and the dilution method of Neufelt is therefore used. At first the capillary pipettes of Wright, and human leucocytes, were made use of with progressive dilutions of the serum and salt dilution and normal serum controls. The titer of the serum is expressed by the highest dilution in the final mixture, which showed more phagocytosis than the controls. Thus the primary serum dilution, 1 in 10, 1 in 100, would become when diluted with equal volumes of leucocytes and bacterial emulsion, 1 in 30, 1 in 300, etc. By this method a rapid inspection of the slides eliminates all the dilutions in which the phagocytosis is marked, and only the controls and those slides on the border line remain to be counted. In the last few months we have adopted the Neufelt method *in toto,* since in practice it takes much less time and is quite simple. The leucocytes are obtained from guinea-pigs after aleuronat injections into the peritoneal cavity, and the mixture of leucocytes, serum and bacteria is made in small test tubes. The serum is inactivated at 56° C. for 30 minutes and the mixture is incubated for two hours at 37°, when smears are made and stained with a polychrome methylene blue.

We have found the strain of typhoid bacillus to be very important. All our old cultures, and even many recently isolated ones, are phagocyted spontaneously to such an extent that little

difference can be seen between the controls and the serum to be tested. After searching through all our stock cultures and many recent isolations we selected strains obtained by blood cultures in the early stages of typhoid fever which are almost completely resistant to spontaneous phagocytosis, and these strains have been transferred at infrequent intervals, and only one out of the several selected has since degenerated to the same condition as the older cultures. With a suitable culture of typhoid, guinea-pig leucocytes and a rather long period of incubation, we found no difficulty in getting regular and well-marked determinations of the phagocytic power of the serum.

The leucocyte count is temporarily but regularly increased after each dose of vaccin. The rise is often to 15,000, and the fall is gradual and reaches normal in about a week.

The accompanying chart shows graphically the percentage of severe (103° F. or over), moderate (100° to 103° F.), mild (up to 100° F.) or absent general reactions in various groups.

The total reactions recorded is 3640 of which 0.9 per cent were severe, 5.7 per cent moderate, 25.3 per cent mild, and 68 per cent absent. The same number of reactions grouped according to doses shows the following:

	1st Dose.	2d Dose.	3d Dose.
Severe	1.0%	1.2%	0.3%
Moderate	7.7	5.6	3.1
Mild	30.7	24.9	18.7
Absent	60.5	68.2	77.8

The reactions of those who have never had typhoid are as follows (1204 persons):

	1st Dose.	2d Dose.	3d Dose.
Severe	0.9%	1.1%	0.4%
Moderate	7.5	5.3	3.0
Mild	31.4	25.6	19.2
Absent	59.9	67.8	77.2

The reactions among those who had had typhoid is as follows (124 persons):

	1st Dose.	2d Dose.	3d Dose.
Severe	1.6%	1.9%	0.0%
Moderate	12.0	10.3	5.4
Mild	25.8	23.2	19.5
Absent	60.4	64.6	75.0

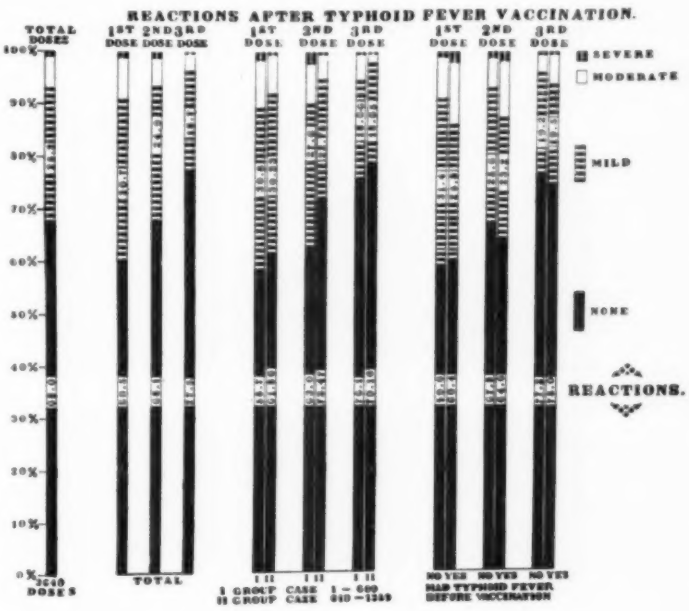
In order to learn whether we were making any progress in eliminating the unpleasant effects of the vaccination, the first 609 cases vaccinated are compared with the last 750. The graphic method shows by a glance at the chart that we have made decided progress in this direction, and that the number of unpleasant reactions has been reduced considerably.

Up to the present time applicants have been vaccinated without regard to age and a few people of 50 or more years of age have been treated, and the reactions have been tabulated in 10-year periods, and it is seen from the accompanying table that the percentage of cases in which the reaction is absent decreases with the increase in age and the percentage of mild reactions increases: there is no very marked difference in the moderate and severe reactions at different ages. On the whole, one may say that the younger the applicant the less marked the general reactions.

THE PERCENTAGE OF DIFFERENT REACTIONS AT VARYING AGES.

Age.	First Dose.				Second Dose.				Third Dose.				
	Absent.	Mild.	Moderate.	Severe.	Absent.	Mild.	Moderate.	Severe.	Absent.	Mild.	Moderate.	Severe.	
0 to 10	73	20	06	00	100	00	00	00	93	07	00	00	15 cases.
10 " 20	80	14	04	01	81	16	01	00	94	03	02	00	97 "
20 " 30	61	31	06	01	71	22	04	01	81	15	03	01	595 "
30 " 40	50	39	09	01	62	26	08	01	73	22	02	01	153 "
40 " 50	42	46	08	01	61	26	07	06	70	29	00	00	24 "
50 " 60	33	60	06	00	46	53	00	00	54	45	00	00	5 "

In children both the local and general reactions are exceedingly mild and cause little or no inconvenience.



The history of the prophylactic use of anti-typhoid vaccin goes back, as we have seen, to 1898, and it is in some ways a matter of surprise that a method which promises so much has been used so little. It can be said that it has scarcely been used outside of the English, German and American armies. The reasons for the failure of the method to become popular in civil life, especially in hospitals, institutions, and among gangs of laborers employed on railroads and public works, are worthy of some study. It will help to place the conditions clearly before us if we consider for a moment the procedure carried out on the appearance of an epidemic of smallpox. In that event all contacts are immediately vaccinated. The newspapers call attention to the presence of the disease and many people seek protection at public vaccinating stations or at the hands of their family physicians. In addition all children must, as a rule, be vaccinated before they can be admitted to school. All recruits for the army and navy

are vaccinated as soon as they are sworn in. These general rules are of course the result of years of experience with smallpox, for at one time vaccination in smallpox was in much the same chaotic condition as vaccination against typhoid to-day. We are met at the very beginning in the case of typhoid with such statements in modern text-books as this:[10]

The immediate effect of the vaccination is to diminish the resistance to infection by typhoid bacilli, and if large doses have been given this diminished immunity may be very marked. With this there is a great increase in both the bactericidal and agglutinating elements in the blood. With small doses the increased immunity is less and persists for a shorter time. This has led Wright to advise the giving of two weaker injections in preference to one strong one. . . . It is evident that it would not be wise to vaccinate during an epidemic as the procedure apparently makes the individual less resistant to infection for a time.

It is difficult to predict to what an extent vaccination against typhoid fever may be used in the future. It would certainly seem wise to carry it out among troops who are going to infected districts. In epidemics it should not be used, as already noted. The troublesome symptoms which occur immediately after the injection should not be considered as a contra-indication.

If we are to be guided by the opinion of this writer we would not be able to use the method in stamping out an epidemic but must confine ourselves to long-range prophylaxis.

Another reason for the lack of appreciation of the value of this measure has been the idea that it produced violent reactions and gives the patient not only a very sore arm but also a good deal of prostration, and often headache, fever and chills. A report published by Flemings, of the German Army, is largely responsible for this. He found that 97.1 per cent of his cases developed fever and that the average was 38.4° C. The highest was 40.3° and the lowest 37.2° C.

There were chills in 63.1 per cent, headache in 61.2 per cent, and vomiting in 19.4 per cent. Loss of appetite occurred in practically all cases. Albuminuria was present in two out of the 91 treated. Herpes labialis occurred in 19.4 per cent.

The vaccin used by Fleming was prepared according to the method of Pfeiffer and Kolle, and is much stronger than ours. They obtain only 5 cc. of finished vaccin from an average agar slant while we get about four times as much, and this excessive dosage is probably responsible for the severe type of general reaction obtained. It is also true that many of the earlier vaccinations, even those carried out by Sir A. E. Wright, were made with quite large doses and there were, no doubt, a good many severe and prostrating reactions. The dosage in the early days was based largely on the result of inoculations in animals, and was to a certain extent misleading as the usual laboratory animals are not susceptible to the disease, and are relatively resistant to the endotoxins. Now that we have found as a result of many thousand vaccinations in human beings, a more suitable and sufficient dose we are no longer troubled to any considerable extent with the severe reactions.

The greatest of all obstacles with which we have to contend, however, is the very prevalent idea of the negative phase: the idea that an individual is more apt to contract typhoid fever for a short time after vaccination than he would have been had he not been immunized. The expression "negative phase" we owe to Sir A. E. Wright, who stated that there is a drop in the anti-toxic and bactericidal content of the blood for a short period following a dose of the vaccin. He quotes Ehrlich and Madsen to the same effect. Reference to his paper will show, however, that he was not dealing with the effect of the first dose, but with the effect of a dose of toxin on an animal already immunized. Ehrlich's and Madsen's studies were made on the effects of the administration of diphtheria and tetanus toxin and not with typhoid or any of the group of bacteria which act through insoluble or endotoxins. There are good reasons for believing that behavior of these two groups of bacteria is quite different. Because a negative phase and increased susceptibility to the toxin developed after a time in horses used for the production of diphtheria antitoxin, we should not infer that a period of increased susceptibility follows the injection of killed typhoid bacilli or any other of the bacteria which do not produce exotoxins.[11] It does not appear that the effect was to diminish the quantity of protective anti-bodies below the normal, but merely somewhat below the level attained during a preceding immunization. In the same paper he gives several curves of the bactericidal power of the blood following anti-typhoid vaccination. In two of these there is shown a decided drop below the normal after the first vaccination, in a third there is a very small negative phase of bactericidal power, and in the fourth there is a complete suppression of the negative phase. Wright's[12] own conclusions as to the practical importance of the law of negative and positive phase in connection with prophylactic inoculations undertaken with living or sterilized vaccins are as follows:

In considering, in the light of individual results obtained in certain series of anti-typhoid inoculations undertaken in actually infected surroundings, the significance of the negative phase of bactericidal power after anti-typhoid inoculation, I have called attention to the fact that the success of these prophylactic inoculations is imperiled where excessive doses of vaccin are administered to patients in actually infected surroundings, or immediately before transference to such surroundings. Basing myself upon information collected in India by the Indian Plague Commission, in connection with Mr. Haffkine's anti-plague vaccination, I made a similar suggestion in connection with this prophylactic inoculation. And I have recently learned that the idea of a risk attaching to the inoculation of large doses of vaccin in infected surroundings suggested itself also to several observers in South Africa who had occasion to watch the effect of the anti-typhoid inoculation there undertaken. If the suggestion made by me in connection with anti-typhoid and anti-plague inoculation are justified, we may not reasonably expect to find indications of an increased susceptibility to smallpox in the period supervening immediately upon the development of vaccinia pocks. It seems to me that such evidence can be found.

A final word on this question will be appropriate. If the risks incidental to the production of a negative phase attach, as I believe they do, to prophylactic inoculations in the case of all septicæmic diseases alike, it is obviously incumbent upon us neither to ignore nor to magnify these dangers, and, above all, to recognize that these risks can be minimized. Let it be observed that the risk of

a negative phase comes seriously into consideration only when excessive doses of vaccin are employed, and when the prophylactic inoculations are undertaken in the actual presence of infection. The remedy lies at hand. It lies in the case where a sterilized bacterial culture is employed in the reduction of the dose. It lies in the case of anti-smallpox vaccination in the reduction of the number of insertions; in other words, in limiting the elaboration of the toxins by diminishing the area of skin surface employed for the culture of the organism of vaccinia.

We see that in Wright's opinion the negative phase is not necessarily associated with every immunization process but is due to avoidable causes, *i. e.*, to excessive dosage. In another place he states that "where a dose of vaccin which is only just sufficient to produce an effect on the blood is administered the negative phase is elided and there is registered only a positive phase."

In the preface [3] he again made the following rather characteristic statement:

When once it had become clear in the course of an investigation into the effect of anti-typhoid inoculation upon the blood, that it would be practicable to *control* the "negative phase" and to confer upon a patient the advantages of immunization without risk or appreciable delay, the thought lay very near that it might prove possible to elicit even after microbes had made good their entry into the body, an immunizing response which would be therapeutically valuable.

I might quote further, if space permitted, from Wright to show that while we should not ignore, neither should we magnify the danger of the negative phase.

I would not take so much of your time in considering the various aspects of the negative phase had it not proven the greatest obstacle to our progress in immunizing the army. As you may know, we have very little typhoid in the service in time of peace. In 1908, the last year for which statistics are available, the admission rate was 294 per 100,000 strength, with a death rate of 23 against a death rate of 52.3 (1906) for Washington, and 34.3 (1906) for Baltimore. The death rate in the army is a little less than half that among the civil population of military age in the registration area of the United States.

The time when officers and men begin to inquire about the benefits of vaccination is after a case or two has occurred or a small company epidemic has broken out. The medical officer is appealed to and he very probably looks up the subject and finds that if he proceeds to immunize the command he will be proceeding contrary to the advice of many authorities. After the epidemic is over and the danger past no one is then interested in the subject and it is dropped.

It will, therefore, be worth while to look upon this problem from another point of view, the experimental one.

R. Pfeiffer, in 1908, summed up our knowledge of the negative phase as follows:

The existence of the so-called negative phase is of considerable importance in the question of protective inoculation against typhoid. The existence of this condition was first asserted by Wright and said to consist in a heightened susceptibility to infection among the inoculated, which begins immediately after injection and lasts until the beginning of the immunity reaction.

This negative phase of Wright's has played a great part in the literature of anti-typhoid inoculation in late years, and it, more than anything else, is to be charged with the reluctance to take up the practical carrying out of inoculations in spite of the undeniable results which are obtained when the practice is carried out in the proper way.

It is really rather remarkable that thorough experimental work on this subject hardly exists. We have before us only the work of Wright and his students, whose method cannot be said to be wholly unobjectionable since it is based principally on the so-called opsonic effect of the serum, whose importance in the production of immunity is not yet really cleared up, and which, therefore, is hardly sufficient grounds upon which to base such very important conclusions.

In the immunization of animals to various toxins it not seldom occurs that as a result of the inoculation of the poison there is a temporary sinking in the curve which represents the variation in the antitoxic titer of the serum, and this has been designated as a negative phase; but it has been very wrongly so-called, since a fall below the normal strength of the serum is not observed which would correspond to a condition of heightened susceptibility as contrasted with the normal. The same criticism might be made of the statement of Kutscher and Hetch, that after the second inoculation the bacteriolytic titer of the serum fell below that produced by the first inoculation; finally, certain clinical observations have been brought forward to prove the existence of the so-called negative phase: Men have been taken sick with an especially severe form of typhoid fever immediately after the inoculation of an anti-typhoid vaccin. There are, however, not a very great number of such cases, so that in drawing conclusions from them a certain amount of caution is necessary.

Theoretically the acceptance of a negative phase is an almost self-evident consequence of the well-known Ehrlich side chain theory.

Really a certain number of the protective bodies present in the normal serum must be anchored at least temporarily in satisfying the receptors of the vaccin which is injected, and so cause a sinking of the bactericidal titer of the serum to appear. The only question is whether this fall with the amount of the vaccin which is used in actual practice is sufficient to call forth a distinct increase in susceptibility to infection. It is known from the investigations of Pfeiffer and Friedberger that in bacteriolysis the amboceptors which are anchored at the beginning of the process, soon become free and again able to combine, that is, they are cut out of the circuit for a short time only. On the other hand, the quantitative relations of the amount of bacterial substance which it is practicable to inject into a man in the shape of a vaccin to the anti-bodies which are normally present in the body, are not such as to occupy any great number of them; so that the temporary anchoring of a certain portion of these anti-bodies by the small quantity of vaccin used would be quite insignificant in comparison to the entire quantity of anti-bodies present in the body. This explanation applies even more forcibly to men who already have an increased immunity due to a previous inoculation when they are subjected to a second dose than it does to normal men. The questions which are here raised are suitable for experimental proof only to a certain degree.

Since 1898, R. Pfeiffer and Marx have followed, by means of approved methods, the changes in the blood serum of rabbits which had received subcutaneously relatively large doses (several cultures) of killed cholera germs. In these experiments a fall in the amount of protective bodies already present in the normal serum has never been observed; on the contrary, there has often been observed even in the first 24 or 48 hours a certain, though small rise, which is brought about by the specific irritation acting on the blood-forming organs so that they begin to pour out the

corresponding secretion. These facts have not been sufficiently considered by the adherents of the negative phase. Quite lately I have, together with Friedberger, attacked this problem. In some experiments which have not yet been published we have completely convinced ourselves that guinea-pigs, which had received under the skin of the back relatively large doses of killed typhoid cultures (doses which reckoned according to the body weight were many hundred times the quantity of vaccin used to immunize men) did not show a diminished resistance to intra peritoneal infection with living typhoid bacteria, but on the contrary showed a distinctly increased resistance, and indeed this increase in resistance appeared within a few hours and was demonstrable up to the moment when, as we know, a secretion of specific amboceptors begins.

In these unequivocal experiments there was, therefore, not the slightest indication of a negative phase. One is reminded of the older experiments of R. Pfeiffer and Isaeff, which led to the conception of a condition of (non-specific) resistance as contrasted to a condition of true (specific) immunity.

In our newer experiments a non-specific resistance which arises as a result of the injection of typhoid culture, plays the principal part in protecting the animal, and this is made quite clear from the fact that the guinea-pigs which had been treated with typhoid were at the same time made more resistant to infection with cholera and *vice versa*. I do not desire to apply these results obtained with animals, without further experimentation directly to mankind, but taking all these things into consideration one must wish before accepting the existence and the significance of the negative phase in mankind, that further experimental data be brought forward.

Emery summarizes the work of Pfeiffer and Friedberger as follows:

They conclude that the fear of a negative phase is exaggerated; and it must not be forgotten that the essence of the "opsonin therapy" consists in administering a dose of vaccin, in the first instance, while the index is low.

There is thus no direct proof that the period of the negative phase is coincident with the period of hypersensitiveness to infection. And when we compare it with the period of increased sensitiveness to toxins we find that whereas the negative phase comes on almost immediately, the hypersensitiveness to toxins or tuberculin, or anaphylaxis to serum, takes some days to develop.

In prophylactic vaccination against cholera we hear nothing of any increase of susceptibility following this immunization. Murata[16] has reported its use in a very wide spread epidemic of the disease in Japan in 1902. There were 1299 cases and 902 deaths, 73.3 per cent. The epidemic began on the 31st of July and lasted until December 23. The vaccination was begun on August 5, that is, within a few days of the beginning of the outbreak and during the progress of the epidemic 77,907 persons were vaccinated; among these there were only six cases per 10,000 while there were 13 or over twice as many among the unvaccinated. Murata does not even mention the negative phase in his report.

It is noteworthy that 10 years' experience with anti-plague vaccination[17] has shown that there is no basis in fact for the hypothesis suggested by Sir A. E. Wright, that a negative phase or period of increased susceptibility might follow the vaccination, and that experience has shown that individuals can be vaccinated on the appearance of an epidemic or at any time during its course, and that the vaccination not only does not predispose to infection, but if given during the incubation period actually mitigates the disease.

It is hardly necessary to do more than mention Wright's views as to a negative phase after vaccination against smallpox to dispose of the question. The contrary view is too firmly established to be shaken.

Victor Vaughan, of Ann Arbor, has informed me that his results have been quite similar to those of Pfeiffer, and that his animals are not more susceptible but more resistant to infection immediately after vaccination.

Col. Leishman[18] informs me that the negative phase in anti-typhoid vaccination is a negligible factor.

During the last two years a considerable number of cases of typhoid fever have been treated with vaccins, and although the therapeutic value of the measure has not been determined, we have at least found out that it does no harm, and that clinically no negative phase follows the giving of vaccins.

Since the introduction of vaccination in the army we have had 135 cases of typhoid among approximately 75,000 men, and only one of these was in a man who had been vaccinated. He received the first dose in New York and left next day for San Francisco. The second dose was received 10 days later at sea. On the 19th day after the first dose he was taken into hospital with typhoid. Infection probably occurred between the administration of the first and second doses while crossing the continent. He ran a mild course, the temperature reached 103° F. once only, and there was no relapse. One other case developed on the same transport in a man who had not been inoculated.

With this exception there have been no cases among the 1400 people immunized.

The procedure has been introduced so recently that it is not yet possible to form any idea of the amount or the duration of the immunity from statistics.

There has been no opposition from the laity and it is felt that anti-typhoid vaccination in the army has successfully passed the introductory stage, and that its use should be rapidly extending among all those whose vocation exposes them to the possibility of typhoid infection.

The following conclusions on this subject seem to be justified:

1. Vaccination against typhoid undoubtedly protects to a very great extent against the disease.

2. It is an indispensable adjunct to other prophylaxis among troops and others exposed to infection.

3. It is very doubtful if there is an increase of susceptibility following inoculation.

4. Vaccination during the disease, for therapeutic purposes, fails to reveal any evidence of a negative phase.

5. The statement that vaccination should not be carried out in the presence of an epidemic is not justified by the facts at hand.

6. The procedure is easily carried out and only exceptionally does it provoke severe general reactions.

7. No untoward results have occurred in this series of 3640 vaccinations.

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NOTES ON NEW BOOKS.

A Manual of Operative Surgery. By SIR FREDERICK TREVES, Bart., F. R. C. S., etc., and JONATHAN HUTCHINSON, F. R. C. S. Third Edition. Vol. I. 745 pages. (*Philadelphia: Lea & Febiger, 1909.*)

Sir Frederick Treves, in the preface to the first edition of his Manual published in 1891, defines its scope in the following words: "The present work concerns itself solely with the practical aspects of treatment by operation, with the technical details of operative surgery, and with such part of the surgeon's work as comes within the limits of a handicraft. . . . . For the selection of particular methods of operating I must hold myself answerable. . . . . I have selected such measures as have appeared to me to be the best, and have made no attempt at encyclopædic completeness."

The work, therefore, derives its chief value from being a faithful statement of the surgical practices of one of the most eminent of English surgeons. The present edition to a certain extent lacks this personal quality, for the editor, Mr. Jonathan Hutchinson, states that "So many additions and alterations have been made in this edition that it is really a new work," and further that "The sections on ovariotomy and hysterectomy have been revised by Dr. H. Russell Andrews, those referring to renal and vesical operations have been revised and extensively altered by Mr. F. S. Kidd and myself, the section dealing with operations on the rectum has been revised and largely rewritten by Mr. A. J. Walton."

The volume covers the fields of abdominal, including gynecological, genito-urinary and rectal surgery. It is written in a very concise and pleasing style and is very easy reading. Wise maxims and bits of good advice abound on every page. The following are examples: "In the handling of a sharp instrument in connection with the human body a confusion of the intellect is worse than chorea." "The actual manipulative part of surgery requires no very great skill, and many an artisan shows infinitely more adeptness in his daily work." "There is no doubt that the fewer the implements to which a surgeon accustoms himself, and the simpler they are, the better." "The surgeon who cannot excise the vermiform appendix without inventing a clamp for the purpose has mistaken his vocation."

It is not the purpose of this review to discuss the wisdom of the various procedures advised in the book. We take it to be a fair statement of the best and most conservative British practice. The writers are frankly dogmatic in statement and make no pretense of giving an extensive review of the literature. It is, therefore, unfair to criticise them adversely for not giving any account at all of many operations which are favorably regarded in this country. Thus Finney's pyloroplasty is disposed of in the following sentence: "The very elaborate plastic operation on the pylorus devised by Finney, an American surgeon, appears to us hardly to require description here." It is their misfortune not to be better acquainted with this admirable operation.

One would think from reading this book that the English surgeon is far more cautious than the American. Two noteworthy instances of this are the very elaborate method for cleaning the skin before operation, and the extreme length of time it is advised to keep patients in bed after operation.

When the writer of such a book as this does refer to the practice of clinics other than his own he is in duty bound to have his statement fair and up-to-date. This the writers of the present work certainly do not always do. In speaking of hernia, they describe as the practice at the Johns Hopkins Hospital an operation which has now not been performed here in many years. The book, on the whole, is very interesting and instructive reading.

W. D. G.

Atlas of External Diseases of the Eye for Physicians and Students. By DR. RICHARD GREEF. Only authorized English translation by P. W. SHEDD, M. D. (*New York: Rebman Company, 1906.*)

No more beautiful and accurate plates ever appeared in any medical atlas than in this atlas of external diseases of the eye by Professor Greef, of the University of Berlin, and the text accompanying the plates is characterized by its simplicity and directness and the therapeutic suggestions are all valuable and can be conscientiously followed. We find much more valuable subject matter than we could reasonably expect in an atlas, and this book will no doubt be a welcome addition to an oculist's library. A good deal more care should have been exercised by the translator in rendering such a valuable work into English and the loose use of the word "eyes" where "lids" are evidently intended, on p. 20, should not have occurred, nor the use of the word "disinfectant" for "antiseptic" on p. 55. We do not like such expressions as "bacillary content"; "inobtrusive treatment"; "treated medicamentally," p. 66; "a wave of pus," p. 74; "superficial morbidity," p. 79; "necrotogenic," p. 79, etc., etc., etc. Yet the author is not at fault, and he presents the medical profession a very excellent and valuable atlas.

B. B. BROWNE, JR.

A System of Syphilis. Edited by D'ARCY POWER, M. B. OXEN, F. R. C. S., and J. KEOGH MURPHY, M. D., F. R. C. S. With an introduction by SIR JONATHAN HUTCHINSON, F. R. S. Vol. III. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

For this volume Professor Osler and Dr. A. G. Gibson have contributed an excellent chapter on "Visceral Syphilis," one of the most thorough in the English language, and admirably illustrated.

"The Clinical Aspects of General Paralysis" is discussed by Dr. Charles A. Mercier, who lays stress on the close relationship of general paralysis and syphilis; all may not agree with him in his views, but none but will be benefited by reading this clear presentation of the question. "Yaws" is described by Professor Aldo Castellani; and, after reading his paper and studying his illustrations, it is hard to believe that the disease has any connection with syphilis. His photographs are splendid, and his description of the disease illuminating. Dr. Stanley B. Atkinson writes on "Some Medico-Legal Associations of Syphilis," and Dr. E. M. Brockbank on "Syphilis and Life Assurance," both valuable papers. The final article is "The Serum Diagnosis of Syphilis," by Dr. Haldin Davis, who gives a full and comprehensive account of the latest work done along this line. All the papers are important contributions, and if the editors succeed as well with the following volumes, the system will be of lasting value.

International Clinics. Edited by W. T. Longcope, M. D. Vol. IV. Nineteenth series. 1909. (*Philadelphia and London: J. B. Lippincott Company.*)

This volume contains a number of timely and well prepared clinical papers on a variety of subjects. It opens with one by Flexner, on "Antimeningitis Serum and the Results of Its Employment." No one is more competent than the author to speak authoritatively on this subject; and to foreigners what he says should prove especially interesting. Charles Green Cumston describes fully "Epiploitis Following the Radical Cure of Hernia," a condition not often recognized by the surgeon; and there are various other papers to appeal to workers in different lines.

Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New Series No. 36. Observations on Rabies, with Especial Reference to an Atrophic Form of the Disease Occurring in Animals. By Major G. Lamb, M. D., I. M. S., and Captain A. G. McKendrick, M. B., I. M. S. Price 9 pence. (*Calcutta: Superintendent Government Printing, India, 1909.*)

This is a brief but carefully prepared report. It describes the passage of the virus of the street through the dog; a peculiar form of rabies seen in rabbits and dogs; the susceptibility of various animals toward fixed rabbit virus; an attempt to immunize monkeys by means of single doses of fixed rabbit virus injected subcutaneously; bactericidal properties of the serum of patients taken both during the course of anti-rabic inoculations and after the treatment had been completed; and protocols. Students interested in the study of rabies should give careful attention to this report.

Practical Points in the Use of X-ray and High-Frequency Currents. By Aspinwall Judd, M. D., etc. (*New York: Rebman Company, 1909.*)

As the author states in his preface, this book is intended for the general practitioner and no attempt has been made at absolute scientific accuracy.

Part I is devoted entirely to descriptions of apparatus and use of the same. This section is to be especially commended as the author describes in detail individual parts of X-ray apparatus and how properly to use them, a subject which is too frequently curtailed in most text-books.

The beginner, by carefully studying this section, will find many valuable hints which will save him much useless worry and even damage of apparatus.

Part II is devoted to radiotherapy and to the therapeutics of high-frequency currents. The author in a brief manner outlines the diseases to which these treatments can be applied. In his endeavors to be brief he has sacrificed some of the details which to the reader seem essential.

Manual of Operative Surgery. By H. J. Waring, M. S., M. B., B. Sc. (Lond.), F. R. C. S. Third Edition. 750 pages. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford University Press.*

The first edition of this Manual appeared in 1898. It was "written with the object of serving as a text-book for the classes held in the Operative Surgery Department of St. Bartholomew's Hospital." The work has apparently been very popular in the English medical schools, as it has been through three editions in 11 years. The author has compressed a great amount of information into his book, which covers the entire field of operative surgery, even ophthalmic operations being included. The subjects of general surgical technique, and the sources of wound infection are also discussed. The style is concise and categorical. It is illustrated with 521 figures, several of which are in color. Many of these are from standard works in special departments of surgery. The book is convenient and not too bulky and deserves a wide-spread popularity.

W. D. G.

Progressive Medicine. Vol. IV. December, 1909. (*Philadelphia and New York: Lea & Febiger.*)

The volume contains chapters on "Diseases of the Digestive Tract," "Genito-Urinary Diseases," "Surgery of the Extremities," "Diseases of Kidneys and Therapeutics," respectively contributed by Edsall, Belfield, Bloodgood, John Rose Bradford of England, and Landis. It is only necessary to note the appearance of the work which is published quarterly and to whose merits attention has frequently been called.

Surgery. Its Principles and Practice. Volume V. Edited by W. W. Keen, M. D., LL. D., Hon. F. C. R. S., Eng. and Edin., etc. Per volume, $7.00 net. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

With this volume this new practice ends, and Dr. W. W. Keen deserves the thanks of the profession for having secured for them this useful work, which for some years to come will be regarded as the standard in the English language, at least by American surgeons. A quarter of this volume is devoted to the "Surgery of the Vascular System," by Rudolph Matas; no better authority could have been selected for the work and as a result the chapter is one of the very best in the entire system and one of the best in the language. That on the "Surgery of the Female Genito-Urinary Organs" is less good, and its bibliography shows a very limited reading on this important subject. These two chapters fill nearly half the book, and the other half is given over to a number of subjects which should have appeared in earlier volumes, but unfortunately were late in coming to the hands of the editor. This gives the volume a rather heterogeneous and padded aspect; it would have been better for the omission of one or two of the chapters. If there is a call for a second edition of this Surgery, it is to be hoped that some one person will be employed to edit the bibliographies which follow the chapters, so that one correct system of abbreviation may be used throughout. Foreign titles are wrongly spelled, capitalized and accented, not to speak of a variety of abbreviations of one word which are startling; for instance, "Chirurgie" appears in this form and in four others—"Chir.," "Chirg.," "Chirur.," and "Chirurg"; "Beiträge," "Beit.," "Beitrag.," and "Beiträg" all occur; and there are many others, as "Deut." and "Deutsch"; "Woch" and "Wochen"; "Arch." and "Archiv"; "Berl." and "Berlin," etc. In a classical work published by a leading house attention should be paid to this detail, for typographical errors are as important to the credit of the work here as in the text.

A Text-book of Experimental Physiology for Students of Medicine. By N. H. ALCOCK, M. D., D. Sc., and F. O'B. ELLISON, M. D. With a preface by E. H. STARLING, M. D., F. R. C. P., F. R. S. Price, $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

"In the revised regulations of the University of London, a syllabus of practical physiology has been prescribed, which is more in accordance with the actual requirements of the student of medicine. The present work is an attempt to put this syllabus into practice." These words taken from the preface by Dr. Starling explain the object of this work, and as he goes on to give his approval of this set of problems, the quality of the work is vouchsafed for, although some teachers would doubtless select other experiments. In this small book there are four lessons on muscle, eleven on circulation, three on digestion, four on respiration, two each on the blood and urine, one on temperature, four on the nervous system, and six on special senses. It is intended for "practical classwork," and if the student masters the principles of these experiments, he will be able to comprehend and treat disease intelligently.

Visiting Nursing in the United States. Containing a Directory of the Organizations Employing Trained Visiting Nurses, with Chapters on the Principles, Organization and Methods of Administration of Such Work. By YSSABELLA WATERS, Henry Street (Nurses') Settlement, New York City. (*New York: Charities Publication Committee, 1909.*)

The directory is issued to show what is being done by trained nurses in every department of social service and philanthropic activity. The author wisely points out the correct principles which underlie this movement, "Purity of motives, integrity of work and broad social conceptions of duty to mankind are . . . . necessary qualities in satisfactorily carrying out the daily routine." She further adds that "visiting nurse associations emphasize the importance of a work organized distinctly for the purpose of supplying trained nurses to give home care to the sick poor and to those of small means." How well this purpose has been put into practical form is shown by the statement that in August, 1909, there were 566 such associations in the United States with 1413 nurses. To those persons who contemplate the establishment of similar organizations in future this volume will be indispensable.

The directory which follows is very carefully compiled and furnishes all the information needed to answer any inquiry in reference to the various societies. The book is a very creditable example of what the trained nurse can do in the line of bookmaking. It is a useful manual for the guidance of all who are planning similar associations in the city or country.

A Handbook of Medical Diagnosis. For the Use of Practitioners and Students. By J. C. WILSON, A. M., M. D., Professor of the Practice of Medicine and Clinical Medicine in the Jefferson Medical College, etc. Illustrated. (*Philadelphia and London: J. B. Lippincott & Co., 1909.*)

This is a voluminous work and contains a large amount of useful information. Some parts might have been omitted, however, without impairing its value, as it is overburdened with detail. The manner of presentation is not novel, and some of the latest work is not referred to, even though otherwise very comprehensive. Thus in discussing tabes and general paresis no reference is found to two points of great practical importance; the occurrence of a positive Wassermann reaction and the characteristic changes in the spinal fluid. The book is profusely illustrated, and should be useful to those who desire general rather than particular information on the subjects treated.

P. W. C.

A Practical Treatise on Ophthalmology. By L. WEBSTER FOX, M. D., LL. D., etc. Illustrated. (*New York and London: D. Appleton & Co., 1910.*)

This is another text-book on ophthalmology, but just what "call" the author heard when he concluded to issue to the medical profession and students this volume has not been ascertained by the reviewer after rather careful perusal. Most of the matter contained therein is presented in more authoritative and convincing form in several other American text-books, and the author has failed to vitalize the book by a sane and definite system of therapeutics. Like to the man overboard, to whom is thrown numerous articles by which he might save himself, so the author offers at random, numerous suggestions from which the reader may possibly select the right ones to treat the patient safely and judiciously. On the other hand he may find to his and to the patient's regret that he made the wrong selection. On practically every subject the author gives evidence that he has not reached a stage of mental tranquility and equipoise as regards the therapeutic measures which he himself prefers and adopts, and the result is that the reader is left in doubt.

Again many of the therapeutic measures which he advocates we do not approve of. For instance, we would not think of advising corrosive sublimate irrigations in such strength as (1-2000) in gonorrhœal ophthalmia; for such a strength would tend to injure and macerate the corneal epithelium, which is already subject to injury by the gonorrhœal pus. In the same disease we would not use eserine if the cornea should become steamy, as the author says he has done during the last few years, nor do we use cold compresses, but we do advocate *the very* frequent *irrigations* with boracic acid in warm water which the author does not emphasize at all in his apparent anxiety to do something with lotions containing *six* ingredients *applied* on cotton pledgets. The author states that in gonorrhœal conjunctivitis the inflammation and œdema may be reduced by . . . . or by incisions of the lids at the outer canthus (p. 145) to relieve pressure on the eyeballs.

We consider it a very serious omission, when he failed to add that this would practically never be necessary. If we continued to call attention to therapeutic suggestions which we do not approve of we would practically have to rewrite the Therapeusis of the entire book, so we will say that we do not approve of salt-injections in iritis, nor calomel dusted on phlyctenular ulcers, nor the use of peppermint water or of quinine in "eye" washes (p. 144), or of rose-water (which is usually kept on hand so long in most drug-shops that it is turbid with bacteria or fungus growth). Considerable fault is to be found with the book in that so many preparations are recommended which are not recognized by the U. S. P., *vide* Boroglycrid, pp. 157, 164, Chinosol, p. 158, Chloretone, Cerevisine. The reviewer believes that ophthalmology can be practiced with splendid success without those preparations which are subject to change in composition at the whim of the manufacturing pharmacist, and which the average druggist does not have sufficient demands for, to warrant him carrying fresh in stock.

There is an unfortunate error in regard to the trial-frame on p. 640, and the remarks made regarding the taking of measurements for spectacles are almost foolish. The dogmatic assertions that "when phlyctenular conjunctivitis is met with in adults there is always a history of ocular involvement in childhood," p. 153, and on p. 238, "In episcleritis the iris is always discolored and sluggish, although no iritis is demonstrated," and on p. 241, "In scleritis there is *marked impairment* of vision," suggest the surprising and "wild" answers seen on some student's examination papers, and we should hardly expect them, set down in cold type, in a "Practical Treatise on Ophthalmology"

published by the professor of eye diseases at a large medical educational institution.

These, then, are some of the faults, and while "the" book is readable, there are no special virtues. As far as the students are concerned, several smaller books cover the field more satisfactorily, and as for the medical men and ophthalmologists, they can dig in the gold mines of four or five text-books of ophthalmology for themselves, with Gray's Anatomy and a good Pathology by their side.

B. B. BROWNE, JR.

Infectious Diseases. A Practical Text-book. By CLAUDE BUCHANAN KER, M. D. Ed., F. R. C. P. Ed., etc. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

The title of this work is exact, it is distinctly practical; and the book itself a most excellent guide. The diseases selected and described by the author are those treated in the City Hospital in Edinburgh, of which he is in charge. They are measles, rubella, scarlet fever, small-pox, vaccinia, chicken-pox, typhus fever, relapsing fever, enteric fever, diphtheria, erysipelas, whooping-cough, mumps, and cerebrospinal meningitis. This is without doubt one of the best of the new Oxford Medical Publications, and a work which should have a large sale. Few can write with more authority then Dr. Ker, and there is no better book on this group of diseases in the English language. The author's style is delightful; he is master of the true "clinical" method of instruction, and his work shows the results of long years of experience and thought. His judgment is sound, as is well marked in his treatment, but each division of his subject is handled with a master's skill. This work should be in the hands of every general practitioner and is suited to American conditions as well as to those of Great Britain. It is thoroughly up-to-date, and the illustrations are as good as can be found. All in all, it is a first-class work, and ranks with the very best. It is a rare pleasure amongst the immense amount of commonplace work to find a book which is preeminent in quality.

BOOKS RECEIVED.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by H. R. M. Landis, M. D. Volume IV. December, 1909. 8vo. 334 pages. Lea & Febiger, Philadelphia and New York.

United States Department of Agriculture. Twenty-fourth Annual Report of the Bureau of Animal Industry. For the year 1907. 8vo. 486 pages. 1909. Government Printing Office, Washington, D. C.

St. Luke's Hospital. Medical and Surgical Reports. Volume I. For 1908 and 1909. Edited for the Medical Board by Austin W. Hollis, M. D. 1909. 8vo. 225 pages. New York.

A Practical Treatise on Ophthalmology. By L. Webster Fox, M. D., LL. D. With six colored plates and three hundred illustrations in text. 1910. 8°. 807 pages. D Appleton & Co., New York and London.

Modern Clinical Medicine. Diseases of Children. Edited by Abraham Jacobi, M. D., LL. D. An Authorized Translation from "Die Deutsche Klinik" under the General Editorial Supervision of Julius L. Salinger, M. D. With 34 illustrations in the text. 1910. 8vo. 828 pages. D. Appleton & Co., New York and London.

The British Guiana Medical Annual. Sixteenth Year of Issue. 1908. Edited by K. S. Wise, M. B., B. S., B. Sc. (Lond. Univ.), M. R. C. S. (Eng.), L. R. C. P. (Lond.) 1909. 8vo. LII + 126 pages. Printed by "The Argosy" Company, Limited, Demerara.

Scientific Memoirs. No. 36. (*New Series.*) By Officers of the Medical and Sanitary Departments of the Government of India. Observations on Rabies: With Special Reference to an Atrophic Form of the Disease Occurring in Animals. By Major G. Lamb, M. D., I. M. S., and Captain A. G. McKendrick, M. B., I. M. S., 1909. Fol. 34 pages. Superintendent Government Printing, Calcutta, India.

A Text-book of Physiology. By William H. Howell, Ph. D., M. D., LL. D. Third edition, thoroughly revised. 1910. 8vo. 998 pages. W. B. Saunders Company, Philadelphia and London.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by W. T. Longcope, M. D. Nineteenth Series, Volume IV. 1909. 8vo. 320 pages. J. B. Lippincott Company, Philadelphia and London.

A Text-book of Diseases of the Ear. By Macleod Yearsley, F. R. C. S., 1908. 8vo. 452 pages. Chicago Medical Book Co., Chicago, Illinois.

Diseases of the Stomach. By S. H. Habershon, M. A., M. D., F. R. C. P. With eight colored and eleven black and white plates. 1909. 12mo. 565 pages. Chicago Medical Book Co., Chicago, Illinois.

Surgery: Its Principles and Practice. By Various Authors. Edited by William Williams Keen, M. D., LL. D. Volume V. With 550 illustrations, 45 of them in colors. 1909. 8vo. 1274 pages. W. B. Saunders Company, Philadelphia and London.

A Text-book on the Practice of Gynecology. By William Easterly Ashton, M. D., LL. D. Fourth edition, revised and enlarged. With 1058 new line drawings illustrating the text. By John V. Alteneder. 1909. 8vo. 1099 pages. W. B. Saunders Company, Philadelphia and London.

A Text-book of the Practice of Medicine. By James M. Anders, M. D., Ph. D., LL. D. Illustrated. Ninth edition, thoroughly revised. 1909. 8vo. 1326 pages. W. B. Saunders Company, Philadelphia and London.

A Text-book upon the Pathogenic Bacteria. By Joseph McFarland, M. D. Sixth edition, thoroughly revised. With 211 illustrations, a number of them in colors. 1909. 8vo. 709 pages. W. B. Saunders Company, Philadelphia and London.

La Cure Radicale de la Hernie Inguinale. Leçons Professées à l'Hôtel-Dieu. Par le Docteur Lucas-Championnière. Avec 53 figures dans le texte. 1909. 8vo. 192 pages. G. Steinheil, Paris.

Oxford Medical Publications. Infectious Diseases. A Practical Text-book. By Claude Buchanan Ker, M. D. Ed., F. R. C. P. Ed. 1909. 8vo. 555 pages. Henry Frowde, London; Hodder & Stoughton, London.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.